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Chronic Kidney Disease at High Altitude

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ABSTRACT

With a prevalence of 10 to 11% in the general population, it is likely that many patients with chronic kidney disease will visit or reside in mountainous areas. Little is known, however, about whether short- or long-duration, high-altitude exposure poses a risk in this patient population. Given that many areas of the kidney are marginally oxygenated even at sea level and that kidney disease may result in further renal hypoxia and hypoxia-associated renal injury, there is concern that high altitude may accelerate the progression of chronic kidney disease. In this review, we address how chronic kidney disease and its management is affected at high altitude. We postulate that arterial hypoxemia at high altitude poses a risk of faster disease progression in those with preexisting kidney disease. In addition, we consider the risks of developing acute altitude illness in patients with chronic kidney disease and the appropriate use of medications for the prevention and treatment of these problems.

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With the increasing popularity of travel to and residence in mountainous regions (*E.G.*, 15% of Colorado citizens live above 2100 m) and the 10 to 11% prevalence rate for adult chronic kidney disease (CKD) in the developed world,[1] it is likely that many people with CKD will visit or reside at high altitude. Although the adverse effects of high altitude are well defined for healthy individuals, little is known about the risks and management strategies for patients with CKD. Even in the healthy kidney, regions of marginal oxygenation arise from the complex structure–function relationships of normal renal physiology. Coupled with emerging evidence of a critical role of intrarenal hypoxia in the pathogenesis of CKD,[2–4] there is reasonable concern that arterial hypoxemia during long-term high-altitude exposure and its neurohumoral responses could worsen intrarenal oxygenation and accelerate progression of CKD to ESRD. In this review, we discuss what is known about the effects of high altitude on patients with CKD.

NORMAL KIDNEY PHYSIOLOGY AT HIGH ALTITUDE

Changes in renal function at high altitude arise from the direct effects of hypoxia on the kidney as well as from multiple compensatory adaptations, including changes in ventilation, cardiac output, sympathetic nervous activity, and erythropoiesis. Urine output and sodium excretion vary with the inspired partial pressure of oxygen (P_{O_2}). Diuresis and natriuresis with accompanying potassium and bicarbonate excretion occur with acute reductions of inspired oxygen (Figure 1) and are mediated by oxygen-sensitive peripheral chemoreceptors.[5,6] Urine and serum osmolality are not altered because volume and solute output rise in parallel.[7] As with the hypoxic ventilatory response mediated by the peripheral chemoreceptors, acute hypoxic diuretic and natriuretic responses during the first 24 to 48 h vary almost 10-fold among individuals. The efferent signaling pathway is not linked to changes in renin, angiotensin, aldosterone, atrial natriuretic peptide, vasopressin, endogenous digitalis-like substances, or inhibition of renal sympathetic tone.[5] This may be due to the known effect of hypoxia to increase nitric oxide (NO) release (*via* stimulation of hypoxia-inducible factor [HIF-1α]), although this has not been formally examined. With severe hypoxia, (fraction of inspired oxygen < 0.1), antidiuresis and sodium retention ensue as a result of intense sympathetic nervous system activation and increased upregulation of angiotensin, aldosterone, and vasopressin.[5] After acclimatization, individuals may again experience diuresis and natriuresis with further elevation in altitude.[8]

Renal blood flow (RBF) increases 8 to 20% during acute hypoxia,[9–11] then returns to baseline after several days.[11,12]

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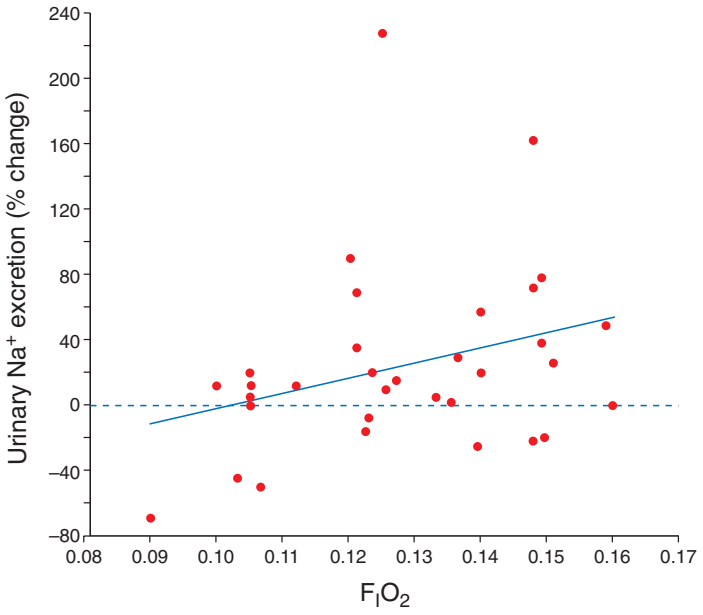

Figure 1. Summary of 32 high-altitude and normobaric hypoxic studies of humans in which sodium excretion was measured between 1 and 24 h of indicated fractional inspired oxygen (F_{IO_2}). Sodium excretion with hypoxia is given as the percentage change above or below the preceding normoxic baseline period. Reprinted with permission from reference.[5]

The effect on GFR is similar.[12,13] In high-altitude residents, RBF is decreased 12% and renal plasma flow by 30 to 40% largely as a result of secondary polycythemia. Because the filtration fraction increases by 39%, however, GFR falls by only 12%.[14,15] In addition, whole organ oxygen delivery, arteriovenous content gradients, and consumption are also maintained at levels equal to sea-level values.[16] Similar findings are present in chronically hypoxic rats.[17]

Because RBF is maintained with acute mild to moderate hypoxia, tubular function remains unaltered.[5] Tubular characteristics, including tubular maximum for glucose, and organic acid and β_2-microglobulin excretion are preserved over a wide range of inspired oxygen concentrations.[10,18,19] Long-term residence above 4500 m may reduce RBF and GFR, but tubular function is maintained because a lower GFR reduces reabsorptive work and oxygen consumption. Sodium excretion in response to angiotensin infusion and the capacity to excrete water and salt loads and maximally concentrate urine with water deprivation or vasopressin are also preserved in chronic hypoxia.[14,20,21] The intact responses to water loading and deprivation occur even though high-altitude natives have lower total body water content than lowlanders (42 *versus* 52% of total body weight).[20]

Acute hypoxia generates acute hypocapnia. Over several days, the kidneys increase bicarbonate excretion to compensate for this respiratory alkalosis, thereby blunting the inhibitory effect of respiratory alkalosis on the hypoxic ventilatory response and improving oxygenation over time at altitude. The compensatory response is largely independent of sodium intake and, thus, does not seem to be linked to the natriuretic effect of hypoxia.[22] Acid-base regulation is maintained in high-altitude natives.[14]

Acute hypoxia causes a two- to threefold increase in urinary protein excretion.[23,24] The mechanism is unclear but may involve changes in capillary permeability,[19] glomerular filtration,[25] or tubular reabsorption of protein.[26] Proteinuria is greater in patients at high altitude who smoke and have hyperlipidemia[27] and in those who develop high-altitude illness.[24,28]

In response to a low arterial P_{O_2}, cortical interstitial cells increase erythropoietin production by stimulating HIF-2α.[29] The subsequent rise in hematocrit helps maintain tissue oxygen delivery. Erythropoietin release begins 1 to 2 h after hypoxic exposure, peaks at 24 to 48 h, and declines to baseline over several weeks as the hematocrit rises and feedback suppression occurs.[30] Subsequent ascents to higher elevations generate new erythropoietin production.[31]

Owing to its high perfusion (1 L/min fully oxygenated blood), the kidney is not conventionally thought to be hypoxic, yet as a consequence of its complex structure–function relationships and marked perfusion–metabolism heterogeneity, which subserve its ability to form a substantial glomerular filtrate and then concentrate or dilute it as needed, regions of the kidney, particularly the outer medulla, are marginally oxygenated even at sea level. Microelectrode and spectroscopic P_{O_2} measurements in normoxic blood-perfused kidneys reveal considerable variations in regional P_{O_2}[32–36] and remarkably low oxygen tensions in the medulla. Although mean cortical P_{O_2} is 40 to 60 mmHg and mean medullary P_{O_2} is approximately 10 to 15 mmHg, there is a wide variation, resulting in 1 to 10% of the cortex and 10 to 30% of the medulla having P_{O_2} values as low as 10 mmHg (Figure 2).[37] In cortical regions, low P_{O_2} values result from a preglomerular oxygen diffusion shunt arising from close proximity of preglomerular arterioles and adjoining

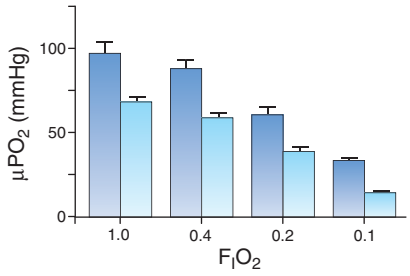

Figure 2. Stepwise reduction in F_{IO_2} resulted in a decline in cortical (dark blue bars) and medullary (light blue bars) microvascular P_{O_2} (μP_{O_2}). Data are means ± SD; $n = 5$. Reprinted with permission from reference.[33]

veins.[34] Three reasons account for the lower medullary P_{O_2}: Reduced perfusion (10%) relative to the cortex, countercurrent circulation that creates an arteriovenous diffusion shunt, and high metabolic demands from mitochondria-rich proximal and medullary thick ascending limb tubular epithelial cells.[38] These regions thus verge on a borderline hypoxic state with little reserve for compromised oxygen delivery or increased metabolic demands. In fact, even in normoxic individuals, medullary regions are vulnerable to hypoxic injury, such as acute tubular necrosis from transient anoxic insults.[39]

Few studies have investigated how arterial hypoxemia might further impair marginal renal oxygenation. In rats breathing 10% O_2 (equivalent to an altitude of 5600 m), mean cortical P_{O_2} declined from 30 ± 6 to 12 ± 2 mmHg, and medullary P_{O_2} declined from 15 ± 3 to 6 ± 1 mmHg.[40] Another study using similar hypoxic conditions showed that the mean cortical P_{O_2} fell from 61 ± 9 to 39 ± 5 mmHg and medullary P_{O_2} declined from 39 ± 5 to 15 ± 2 mmHg.[33] This study also found that 10% O_2 increased the fraction of cortex below 7.5 mmHg from 5 to 62% and the fraction of medulla below the same threshold from 10 to 76% (Figure 3). Reflecting this hypoxic stress, healthy rats, after 6 h at an equivalent altitude of 5600 m, demonstrated subtle microvascular (endothelial cell swelling) and tubulointerstitial injury, inflammation, and fibrosis involving primarily the medulla but also the cortex.[41] To place these results in perspective, 5600 m is well above the highest permanent human settlements and is generally reached only by skilled mountaineers; there are no data for more relevant altitudes of 2500 to 4500 m.

Other factors that may exacerbate renal hypoxia include anemia and hypertension. Severe normovolemic hemodilution (hemoglobin 7.7 g/dl) in healthy rats reduced cortical microvascular P_{O_2} from 70 to 37 mmHg and medullary P_{O_2} from 53 to 28 mmHg.[42] The combined effects of anemia and hypoxemia on renal oxygenation may be more severe in diseased kidneys, because, as nephrons are lost, oxygen consumption in remaining hyperfunctioning nephrons increases.[43] Hypertension may also create further hypoxic stress as suggested by data in normoxic hypertensive rats, in which renal cortical P_{O_2} was 10 mmHg lower and O_2 cost of Na^+ reabsorption was higher than in normotensive rats,[44] possibly as a result of reduced NO production from decreased NO synthase expression.[45]

Although many regions of the "nor-

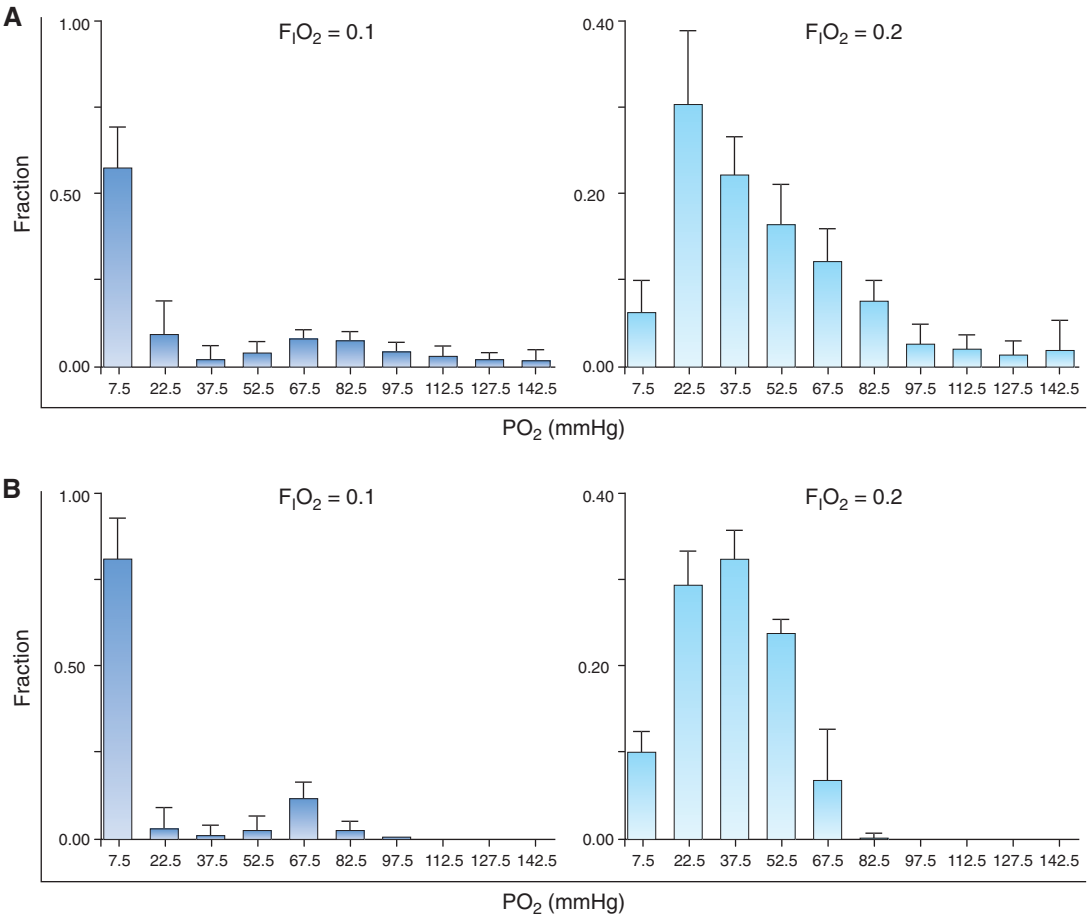

Figure 3. Histograms showing oxygen distributions in the cortex (top) and outer medulla (bottom) of the rat kidney at 10 and 20% inspired oxygen. Reprinted with permission from reference.[33]

moxic" kidney are at the threshold of classic "hypoxia," there is little evidence of subsequent injury or altered function in individuals without kidney disease at sea level and/or high altitude. The protective cellular mechanisms include activation of hypoxia-induced transcription factors (HIF-1α and HIF-2α), which stimulate production of erythropoietin, heme oxygenase (generating the antioxidant carbon monoxide), inducible and endothelial NO synthase–mediated NO production, enzymes, and angiogenic factors,[46] all of which improve O_2 delivery and/or utilization. In addition, the acute natriuretic effect of hypoxia may be protective by decreasing the metabolic work of sodium reabsorption and oxygen consumption. The protective mechanisms engaged with acute hypoxic exposure, including HIF production, may not be sustained with chronic hypoxia[47] and aging,[48] which, in turn, lead to progressive microvascular loss as a result of decreased expression of vascular endothelial growth factor and other cytoprotective molecules.[41]

PATIENTS WITH KIDNEY DISEASE AT HIGH ALTITUDE

To date, few studies have addressed the effects of acute or chronic altitude exposure on patients with preexisting kidney disease. It is unlikely that substantive pathophysiologic studies will be done in CKD at sea level compared with high altitude for reasons of low number of study patients and various ethical reasons. Drawing on the limited available literature and an understanding of the pathophysiology of kidney disease, it is possible, however, to draw tentative conclusions about potential outcomes at high altitude.

Because renal insufficiency impairs urinary concentration and dilution capacity, there could be an increased risk for either volume depletion or overload. Although there is no direct evidence of impaired diuretic responses to hypoxia in patients with CKD, there is some evidence that hemodialysis patients may be at increased risk for volume overload, which may predispose to pulmonary edema and greater arterial hypoxemia. Although patients with lesser degrees of renal insufficiency have not been studied, dialysis-dependent patients at a modest altitude of 2000 m for 2 wk had greater weight gain (0.7 ± 0.3 kg) between dialysis sessions than at 576 m.[49] The cause of this greater weight gain was not investigated.

As a result of impaired erythropoietin production and shortened red cell survival,[50] patients with CKD do not have the expected erythropoietic response to high altitude and show little to no change in hemoglobin concentration, reticulocyte count, and erythropoietin production over 2 wk at altitudes between 2000 and 4600 m.[51–53] Reduced oxygen delivery arising from failure to increase red cell mass may be partially mitigated by changes in hemoglobin–O_2 affinity, but limited data do not consistently demonstrate significant changes in 2,3 diphosphoglycerate or hemoglobin P50.[51,52] Whereas hematocrits of 30 to 34% may be adequate at sea level, the impaired hematologic compensation at high altitude may decrease oxygen delivery and limit physical activity.

Last, patients with CKD often have coexisting cardiovascular disease from comorbidities such as diabetes and hypertension,[54] which put them at risk for cardiac complications at high altitude. The interaction between heart disease and high altitude has been reviewed elsewhere.[55]

Travel to high altitude predisposes all individuals to several acute illnesses: Acute mountain sickness (AMS), high-altitude cerebral edema, or high-altitude pulmonary edema (HAPE). The clinical features and management of these diseases have been reviewed elsewhere[56–58] and are summarized in Tables 1 and 2, respectively. Unfortunately, no studies have evaluated the risks of these illnesses in patients with CKD and whether proven prophylactic therapies for healthy people are effective in this population.

From a theoretical standpoint, by stimulating ventilation and increasing arterial P_{O_2}, the mild metabolic acidosis of renal insufficiency might protect against AMS, assuming that all other aspects of their kidney disease have little to no impact on acute altitude tolerance. All individuals develop a hypoxic ventilatory response at high altitude, which results in hypocapnia and respiratory alkalemia. The ventilatory response is blunted to some degree by the alkalemia, but the full response is restored over a period of 1 to 2 d by renal compensation. Any preexisting metabolic acidosis, however, may help maintain greater ventilation during the initial period at high altitude and better defend the arterial P_{O_2} when compared with a patient who has normal renal function and will require more time or the use of the carbonic anhydrase inhibitor acetazolamide to reach similar levels of bicarbonate loss.[59] Given that a poor hypoxic ventilatory response at high altitude may predispose to AMS,[60–62] mild metabolic acidosis might, therefore, be protective.

Despite this potential protective effect, several aspects of CKD may heighten the risk for altitude illness. Anemia could decrease oxygen delivery and predispose to AMS. Furthermore, metabolic acidosis enhances hypoxic pulmonary vasoconstriction,[63] which, given the central role of exaggerated hypoxic pulmonary vasoconstriction in the pathophysiology of HAPE, could unmask or exacerbate this acute altitude illness.[57] In ESRD, there is also a 40% prevalence of mild to moderate pulmonary hypertension of unknown cause.[64] Because HAPE can develop in patients with various forms of pulmonary hypertension,[65–67] patients with ESRD and similar pulmonary hemodynamics may have a heightened risk for this complication. Whether the prevalence of pulmonary hypertension is as high in patients with CKD before dialysis has not been studied.

Chronic systemic hypoxia associated with long-term residence at high altitude may also contribute to renal progression in patients with CKD. Renal hypoxia has a central role in the progression of renal insufficiency.[2–4] The mechanisms by which this effect occurs are displayed in Figure 4.[2] Glomerulosclerosis and tubulointerstitial disease damage renal arte-

Table 1. Summary of clinical features and management of acute high-altitude illnesses[a]

Illness	Epidemiology	Clinical Features	Prevention	Treatment
AMS	Affects 22 to 50% of travelers to 1850 to 4200 m Incidence higher at higher elevations Onset of symptoms within 6 to 10 h of ascent	Headache plus one or more of the following: Nausea, vomiting, lethargy, poor sleep, light-headedness Normal neurologic examination and normal mental status	Slow ascent (above 2500 m, limit increases in sleeping elevation to 300 to 400 m/d Avoid overexertion Acetazolamide or dexamethasone	Stop ascending Nonnarcotic pain relievers for headache Antiemetics Acetazolamide Descend if symptoms do not improve in 1 to 2 d or worsen on appropriate treatment May continue ascending if symptoms resolve
HACE	Affects 0.1 to 1.0% of travelers to elevations above 3500 m Most affected individuals have preceding AMS symptoms	Preexisting AMS or HAPE symptoms Ataxia, altered mental status lassitude, coma Potentially fatal if not recognized and treated promptly	Slow ascent Avoid overexertion Acetazolamide or dexamethasone	Descend until symptoms resolve If descent not possible, then supplemental oxygen or a portable hyperbaric chamber Dexamethasone; consider adding acetazolamide
HAPE	Affects 0.2 to 8.0% of travelers between 2500 and 5500 m with greater incidence at higher elevations and with faster ascent Occurs within 2 to 5 d of ascent Can occur without preceding AMS	Mild disease: Decreased exercise performance, dry cough Severe disease: Dyspnea with minimal exertion or at rest; cough with pink, frothy sputum; cyanosis May see concurrent signs or symptoms of AMS or HACE Potentially fatal of not recognized promptly	Slow ascent Avoid overexertion Nifedipine Salmeterol can be used as adjunctive therapy but should not be used alone	Descend until symptoms resolve; avoid overexertion on descent If descent not possible, then supplemental oxygen or a portable hyperbaric chamber Nifedipine (may not be necessary if supplemental oxygen available) May consider sildenafil as add-on or alternative, but data on efficacy are lacking

[a]HACE, high-altitude cerebral edema.

rioles and peritubular capillaries, leading to diminished vascular supply to the tubules.[68] Interstitial fibrosis compounds the hypoxia by altering the diffusion distance between viable vessels and remaining functional tubules. In animal models of renal injury, semiquantitative intrarenal P_{O_2} measurements revealed greater intrarenal hypoxia, beyond that detected normally in the medulla of healthy kidneys.[4] Severe hypoxia activates fibroblasts[69] and induces tubular epithelial-mesenchymal transition.[2,70] Chronic hypoxia also increases expression of thrombospondin 1, an antiangiogenic factor, decreases expression of vascular endothelial growth factor,[71] and triggers production of hypoxia-inducible transcription factors whose downstream targets exert both pro- and antiapoptotic effects.[3] Finally, hypoxia produces oxidative stress in the rat kidney without a parallel upregulation of antioxidant enzymes.[72] In humans, this effect is reflected by increased urinary excretion of 8-isoPGF2a, an oxidation product of arachidonic acid.[73]

Given that proteinuria is a marker of and possible contributor to the progression of kidney disease,[74,75] increased protein excretion seen at high altitude may also be problematic. Of additional concern is that protein reabsorption may carry high energy and, therefore, oxygen costs for the kidney. Recent data suggested that as the healthy kidney filters nephrotic-range amounts of albumin, the work of near-complete retrieval by the proximal tubule may not be trivial.[76] Because endocytotic protein reabsorption requires energy,[77] increased protein reuptake could lower intrarenal P_{O_2}. Tubular cells are also activated by luminal protein to produce chemoattractants, proinflammatory and profibrotic cytokines, and matrix proteins,[78] which stimulate interstitial inflammation and fibrosis, processes that might also increase local oxygen consumption and decrease intrarenal P_{O_2}.

These considerations lead us to propose that long-term high-altitude residence in patients with CKD may lead to faster progression to ESRD when compared with sea-level residence. Limited

Table 2. Dosing of altitude illness medications in patient with and without CKD

Medication	Normal Individuals	Renal Insufficiency
Acetazolamide	AMS prevention: 125 or 250 mg twice daily AMS and HACE treatment: 250 mg twice daily[56]	With GFR 10 to 50 ml/min, limit dosing to every 12 h Use is contraindicated in patients with GFR <10 ml/min[98] Also avoid with preexisting metabolic acidosis, hypokalemia, hypercalcemia, and hyperphosphatemia or nephrolithiasis[99,100]
Dexamethasone	AMS prevention: 2 mg every 6 h or 4 mg every 12 h AMS treatment: 4 mg every 6 h (orally, intravenously, or intramuscularly) HACE treatment: 8 mg once then 4 mg every 6 h (orally, intravenously, or intramuscularly)[56]	No contraindications and no dosage adjustments necessary Given issues with acetazolamide, should be considered the safest option for preventing or treating AMS and HACE in patients with nondiabetic CKD
Nifedipine	HAPE prevention: 30 mg of sustained-release version every 12 h HAPE treatment: 30 mg of sustained-release version every 12 h[56]	No contraindication and no dosage adjustments necessary Given issues with sildenafil and tadalafil, should be considered the safest option for HAPE treatment and prophylaxis in patients with CKD
Tadalafil	HAPE prevention: 10 mg twice a day[101] HAPE treatment: 10 mg twice a day (efficacy not established in clinical studies)	With GFR 30 to 50 ml/min, use 5-mg dose once a day, maximum 10 mg in 48 h[102] With GFR <30 ml/min, no more than 5 mg one time[102,103]
Sildenafil	HAPE prevention: 50 mg three times daily (efficacy not established in clinical studies) HAPE treatment: 50 mg three times daily (efficacy not established in clinical studies)	With GFR <30 ml/min, use 25 mg three times a day[104]
Salmeterol	HAPE prevention: 125 mcg twice daily[105]; generally used as add-on therapy and not as monotherapy HAPE treatment: 125 μ g twice daily (efficacy not established in clinical studies)	No contraindication and no dosage adjustments necessary

reports suggested that this concern may be warranted. Navajo Indians living at altitude between 1600 and 3200 m, for example, have a four-fold higher rate of ESRD than the average American population and twice that of all Native Americans, most of whom live at lower elevations.[79] Although other factors including diabetes, income, and access to medical care were considered possible determinants in this study, the role of altitude was not considered. A comparison of outcomes in patients with type 2 diabetes and nephropathy living at sea level and at an elevation of 1700 m showed that despite similar glycemic control, high-altitude residents had greater protein excretion (146 *versus* 89 μg/min), higher prevalence of proteinuria (57 *versus* 33%), higher serum creatinine levels (1.04 *versus* 0.84 mg/dl), and lower GFR (83 *versus* 91 ml/min) than the sea-level residents[80]; however, this study did not include data on disease progression or the need for dialysis.

In the absence of direct evidence for an adverse effect of high altitude on CKD progression, one might consider diseases causing nephropathy and evaluate whether their control is worse at high altitude. The data on glycemic control in patients with diabetes[81,82] and BP control in nonhypertensive individuals[83–86] at high altitude are mixed. No equivalent studies have been undertaken of individuals with baseline hypertension. The important point is that some individuals do experience loss of glycemic and BP control that could lead to decline of renal function.

PHARMACOLOGY AT HIGH ALTITUDE IN PATIENTS WITH KIDNEY DISEASE

With both short- and long-term high altitude exposure, consideration should be given to the proper management of patients' preexisting medications and the selection of medications for the management of high-altitude illness. Patients who have CKD and ascend to high altitude for short periods should remain on their regular medications, and, in most cases, dosage adjustments should not be necessary. Those on diuretic therapy should be advised to monitor their weight daily and increase their diuretic dosage accordingly if weight gain occurs or if fluid retention develops with AMS. Given the uncertainty regarding BP and glycemic control at high altitude, we recommend close monitoring of any patient with CKD, with the anticipation that further treatment might be necessary in some individuals. Analgesia with nonsteroidal anti-inflammatory drugs should be avoided because of their ability to inhibit cyclo-oxygenase–mediated renal vasodilation (reduced O_2 delivery) and stimulate sodium reabsorption (increased O_2 consumption).

The impact of greater proteinuria at high altitude[80] is unknown, but, because proteinuria is associated with progressive renal function decline,[74,75] it may be important to limit its increase with angiotensin-converting enzyme (ACE) inhibition.[87] For patients who are already on an ACE inhibitor, one might add an angiotensin II receptor blocker, because combined therapy can further decrease proteinuria.[88,89] Although renin-angio-

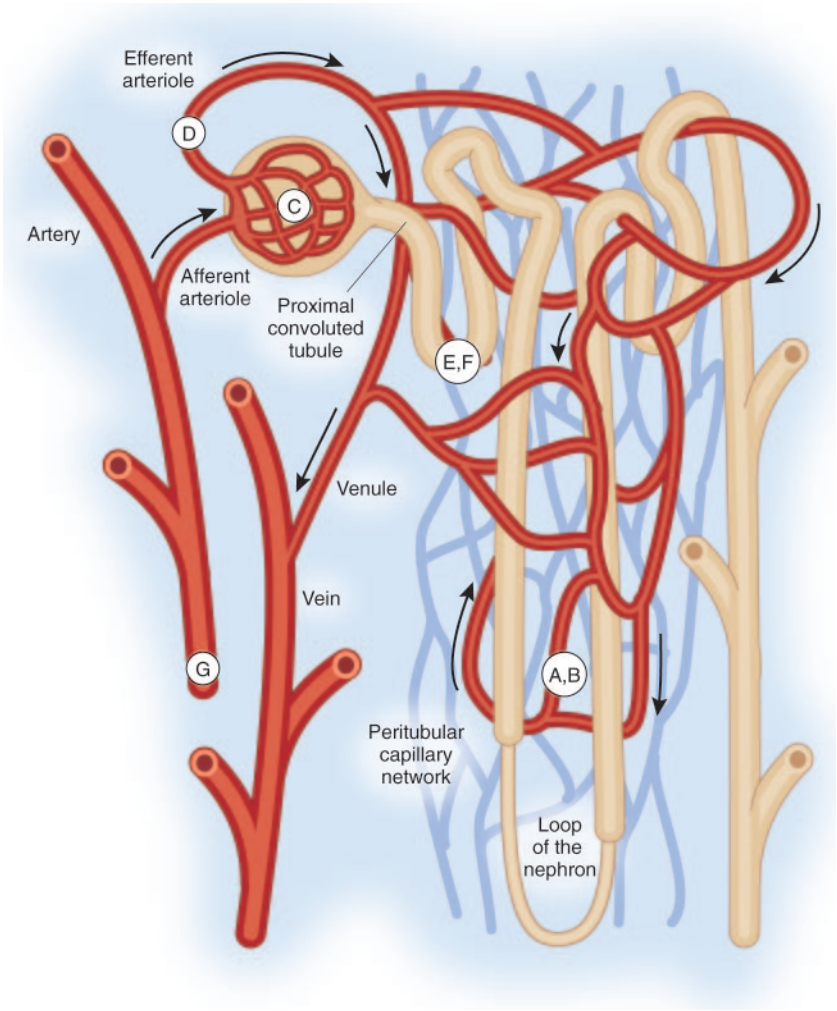

Figure 4. Multiple mechanisms of chronic hypoxia in the kidney. (A through G) Mechanisms of hypoxia in the kidney of patients with CKD include loss of peritubular capillaries (A), decreased oxygen diffusion from peritubular capillaries to tubular and interstitial cells as a result of fibrosis of the kidney (B), stagnation of peritubular capillary blood flow induced by sclerosis of "parent" glomeruli (C), decreased peritubular capillary blood flow as a result of imbalance of vasoactive substances (D), inappropriate energy use as a result of uncoupling of mitochondrial respiration induced by oxidative stress (E), increased metabolic demands of tubular cells (F), and decreased oxygen delivery as a result of anemia (G). Reprinted with permission from reference.[2]

tensin system blockade blunts renal erythropoietin formation and possibly responsiveness,[90,91] we do not believe it is warranted to withhold ACE inhibitors or angiotensin II receptor blockers at high altitude. Instead, these medications can be used with close follow-up of the patient's hematologic status, BP, and erythropoietin requirements.

Patients on multiple medications for BP control should consider avoiding treatment with nifedipine or other dihydropyridine calcium channel blockers, which can increase proteinuria.[92,93] Although tolerable for a few days if nifedipine use is necessary for HAPE prophylaxis or treatment, a sustained increased proteinuria at high altitude would be of concern.

Although it is obvious that anemia and failure to mount an erythropoietic response at high altitude may be problematic for patients with CKD, the appropriate erythropoietin dosing and hemoglobin goal are unknown. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines[94] limit sea-level hemoglobin levels to 11 to 12 g/dl because of concerns of hypertension, thrombosis, and increased cardiovascular mortality with higher targeting. Interestingly, despite their suppressed erythropoietin responses at high altitude, studies of patients with CKD found they needed smaller dosages compared with sea-level requirements and had more thrombotic events and hypertension than with conventional dosing.[95,96] These surprising findings therefore preclude any firm recommendations beyond that of close monitoring of hematocrit and erythropoietin dosage.

Although undertaking an appropriately slow ascent remains the best means to prevent high-altitude illness and descent remains the most effective treatment, pharmacologic measures are sometimes necessary for these purposes. Table 2 presents dosing recommendations for the standard medications used in the prevention and treatment of altitude illness for patients with CKD. These recommendations and their rationale have been reviewed more thoroughly elsewhere.[97] Physicians should also consider a supervised trial of any prophylactic medication deemed necessary to determine whether it can be tolerated before travel to high altitude.

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

Limited available data suggest that patients with CKD can tolerate short-term stays at modest altitudes, but theoretical considerations point to a faster progression to ESRD. Further research is warranted to define these risks better and should include basic research on the effects of clinically relevant inspired P_{O_2} levels on renal function; well-designed epidemiologic studies to address critical factors such as BP, hematocrit, erythropoietin dosing, proteinuria, and rate of GFR decline between high-altitude and low-altitude populations; and clinical trials designed to assess the best means for reducing proteinuria and slowing kidney disease progression at high alti-

tude. Finally, studies on acute altitude illness should include patients with CKD to permit these patients to enjoy the mountain environment more safely.

DISCLOSURES

None.

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