Nephrol Dial Transplant (2001) 16: 2176–2180

Nephrology Dialysis Transplantation

Original Article

Hyperbaric oxygen in the treatment of calciphylaxis: a case series

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Abstract

Background. Calciphylaxis, also referred to as calcific uraemic arteriolopathy, is a syndrome associated with end-stage renal disease (ESRD), and causes necrotic skin ulcers, often leading to a fatal outcome. Hyperbaric oxygen (HBO_2) therapy has been used to enhance wound healing, but its role in the treatment of calciphylaxis is unclear.

Methods. We undertook a retrospective study of patients on renal replacement therapy with biopsy-proven calciphylaxis who were treated with HBO_2 between March 1997 and February 2000.

Results. Five patients were treated with HBO_2: three patients were on continuous ambulatory peritoneal dialysis (CAPD) and two were on chronic haemodialysis therapy. None of the patients had uncontrolled hyperparathyroidism and none underwent parathyroidectomy. The patients each received 25–35 treatments of HBO_2 at 2.5 atmospheres for 90 min per treatment. Two of these patients had complete resolution of extensive necrotic skin ulcers, with no adverse effects of HBO_2 therapy. Both had improvement in wound area transcutaneous oxygen pressure ($P_{tc}O_2$) with administration of 100% oxygen when measurements were taken at normobaric and hyperbaric pressures. In the other three patients receiving HBO_2, the skin lesions did not resolve. $P_{tc}O_2$ was measured in two of these patients, neither of whom showed improvement with 100% oxygen administered at normobaric pressure.

Conclusions. The data support a role for HBO_2 in the treatment of some patients with calciphylaxis, particularly as in the absence of uncontrolled secondary hyperparathyroidism there are few therapeutic options.

Keywords: calciphylaxis; dialysis; hyperbaric oxygen; renal failure

Introduction

Calciphylaxis (also referred to as calcific uraemic arteriolopathy) is a syndrome of small vessel calcification of unknown aetiology causing painful violaceous skin lesions that progress to non-healing ulcers and gangrene. It is observed mainly in patients with end-stage renal disease (ESRD), with a reported prevalence of 1–4% of patients on chronic haemodialysis [1,2]. An increasing incidence has been noted by some centres [3,4]. Although parathyroidectomy has been advocated as a treatment for calciphylaxis in some cases [2,5–9], other studies have not found this to be effective [1,3,10–12]. Indeed, the mortality from calciphylaxis remains between 60 and 80% [1,11], with most patients dying of sepsis from secondary infection of the calciphylaxis wounds [1,8,24].

Hyperbaric oxygen (HBO_2) treatment consists of breathing 100% O_2 at a pressure higher than ambient pressure (1 atmosphere absolute) while the patient is situated inside a sealed treatment chamber. HBO_2 has been used with some success in the treatment of select problem wounds, defined as those that fail to respond to established medical and surgical management. Problem wounds are often severely hypoxic with transcutaneous oxygen pressure ($P_{tc}O_2$) of 5–20 mmHg compared with healthy control tissue $P_{tc}O_2$ of 30–50 mmHg [13]. Healing is impaired when tissue O_2 tension is below 20 mmHg, and restoration of tissue PO_2 to normal or above normal enhances fibroblast proliferation and collagen production as well as angiogenesis. Hypoxia also hinders O_2-dependent polymorphonuclear leukocyte-mediated bacterial killing of the aerobic organisms most commonly found in wound infections [14].

A beneficial effect of HBO_2 in the treatment of calciphylaxis has been noted in several case reports [15–17]. For example, Vassa *et al.* [15] reported one case of a woman on continuous ambulatory peritoneal dialysis (CAPD) suffering from lower extremity calciphylaxis who failed to improve after parathyroidectomy but then experienced healing of the skin lesions after 38 sessions of HBO_2 therapy. Similarly, Dean and Werman [16] reported a case of a haemodialysis

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patient with lower extremity calciphylaxis who responded to 7 weeks of HBO_2 treatments after parathyroidectomy and wound debridement had failed. Because of the poor prognosis of this condition, we evaluated our experience at the Ottawa Hospital in a retrospective study of five patients on renal replacement therapy who were treated with HBO_2 for biopsy-proven calciphylaxis.

Methods

Five patients at the Ottawa Hospital on renal replacement therapy with biopsy-proven calciphylaxis were treated with HBO_2 during the period of March 1997 to February 2000. These cases were retrospectively studied. The patients were identified through the Hyperbaric Unit patient database at the Ottawa Hospital. Patient characteristics (age, gender, mode of dialysis, time on dialysis, distribution of lesions of calciphylaxis, serum levels of calcium, phosphate, PTH, and albumin) were obtained, and response to management was documented. Serum intact PTH was measured by radioimmunoassay. The patients were treated with HBO_2 at 2.5 atmospheres absolute for 90 min, 5 days per week for 5–7 consecutive weeks. At the wound site, $P_{tc}O_2$ was measured in four patients on both room air and on 100% O_2 normobaric by non-rebreathing mask to quantitatively assess O_2 availability to tissue. The skin lesions in patients treated with HBO_2 were photographed at the beginning of therapy and at various stages in their course. Surgical wound debridement was performed and antibiotics were administered as indicated. No specific changes were made to the $CaCO_3$ or vitamin D treatment regimens. Resolution of the calciphylaxis was considered as healing of necrotic areas, with presence of granulation tissue, followed by a reduction in wound size and eventual scar formation.

Results

The characteristics of the five patients are listed in Table 1. The patients are numbered to group them by outcome, and not in the temporal order in which they were treated. In each of the patients, the diagnosis of calciphylaxis was made by wound biopsy, which revealed medial calcification of arterioles with thrombosis, necrosis of adipose and connective tissue, and minimal lymphocytic infiltration (Figure 1). The mean age was 50.8 years, with four females and one male patient. Four of the five patients had either Type 1 or 2 diabetes mellitus, and four were considered to be obese. All five patients were Caucasian. The renal replacement therapy was CAPD in three patients, and haemodialysis in two. The average time on dialysis was 20.2 months. All but one patient was on $CaCO_3$ and/or vitamin D therapy for the treatment of secondary hyperparathyroidism, and no changes were made to their treatments. Two patients (#2 and #3) were on warfarin therapy for atrial fibrillation and mitral valve replacement, respectively, and anticoagulation was continued in both.

Table 1. Patient characteristics and laboratory values

Patient	Age (years)	Sex	Diabetes mellitus	Obesity	Mode of renal replacement	Months on dialysis	$CaCO_3$ use	Vitamin D use	Wound distribution	PTH (ng/l)	Ca (mg/dl)	PO_4 (mg/dl)	Alb (g/l)	$P_{tc}O_2$ on room air mmHg	$P_{tc}O_2$ on 100% O_2 mmHg
1	45	M	No	Yes	HEM	25	No	No	Distal leg	51.6	8.42	7.46	2.7	13	327 at 2.5 atm.
2	50	F	Yes	Yes	HEM	10	Yes	Yes	Abdominal pannus	9.6	8.94	2.97	2.4	7	33 at 1 atm.
3	61	F	Yes	Yes	CAPD	24	Yes	Yes	Trunk, proximal thigh, distal legs	43.9	10.02	4.86	2.4		
4	54	F	Yes	Yes	CAPD	24	Yes	Yes	Trunk, proximal thigh	100.3	10.42	4.49	2.7	18 at 1 atm.	
5	44	F	Yes	No	CAPD	18	Yes	No	Right distal leg, circumferential	178.8	8.82	4.24	2.5	1	10 at 1 atm.

CAPD, continuous ambulatory peritoneal dialysis; HEM, haemodialysis; $CaCO_3$, calcium carbonate; PTH, parathyroid hormone (reference range 10.5–65.0 ng/l); Ca, serum calcium (reference range 9.0–10.5 mg/dl); PO_4, serum phosphate (reference range3.0–4.5 mg/dl); Alb, serum albumin (reference range 3.5–5.5 g/dl); $P_{tc}O_2$, transcutaneous oxygen pressure; HBO_2, hyperbaric oxygen; Atm., atmosphere; n/a, not applicable.

The laboratory findings are also summarized in Table 1. The average serum PTH level was 76.8 ± 65.5 ng/l (reference range 10.5–65.0 ng/l), and no patients had uncontrolled hyperparathyroidism or elevated serum calcium × serum phosphate product. The mean serum albumin level was 2.54 ± 0.15 g/l, with all patients demonstrating hypoalbuminaemia (a serum level < 3.5 g/l). A variety of organisms were cultured from the calciphylaxis wound sites, with four of five patients demonstrating growth of Enterococcus species.

The clinical course of the patients is presented in Table 2. Of the five patients with calciphylaxis, all received a full course of HBO_2 therapy. Two of these (patients #1 and #2) had excellent responses with complete resolution of the skin ulcers (Figures 2 and 3). Healing occurred during the period of HBO_2 treatment in patient #1, and weeks after treatment was completed in patient #2. Neither patient required skin grafting. Transcutaneous oximetry was performed at the wound sites of both patients. Improved tissue oxygenation (Table 1) was observed with HBO_2 in patient #1 with $P_{tc}O_2$ rising from 13 mmHg on room air at 1 atm. to 327 mmHg on 100% O_2 at 2.5 atm. In patient #2, $P_{tc}O_2$ was performed at 1 atm. only. On room air, $P_{tc}O_2$ was 7 mmHg, and while breathing 100% O_2, $P_{tc}O_2$ rose to 33 mmHg.

Three patients who received full courses of HBO_2 did not experience improvement of their calciphylaxis lesions. All three patients (#3, #4, and #5) had some reduction in areas of wound necrosis with some tissue healing, but two patients (#3 and #4) ultimately requested withdrawal of care because of severe intractable pain and development of other medical complications. Measurement of $P_{tc}O_2$ for patient #4 revealed involved areas, which failed to achieve adequate $P_{tc}O_2$

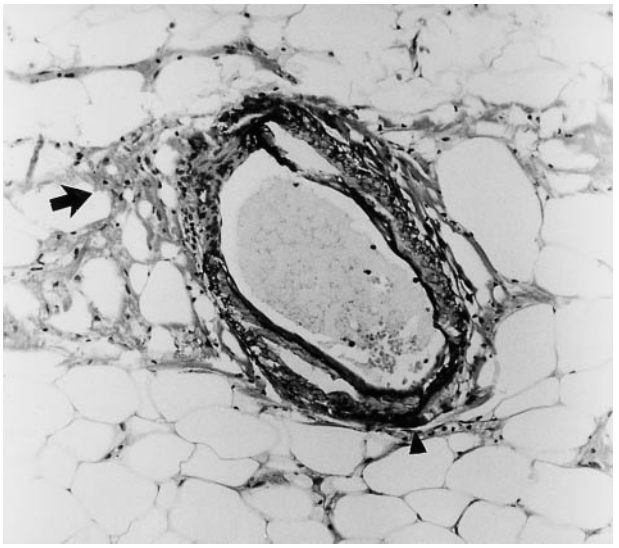

Fig. 1. Biopsy of calciphylaxis wound of patient #2: extensive medial calcification in small muscular arteries (arrowhead) and adjacent fat necrosis (small arrow).

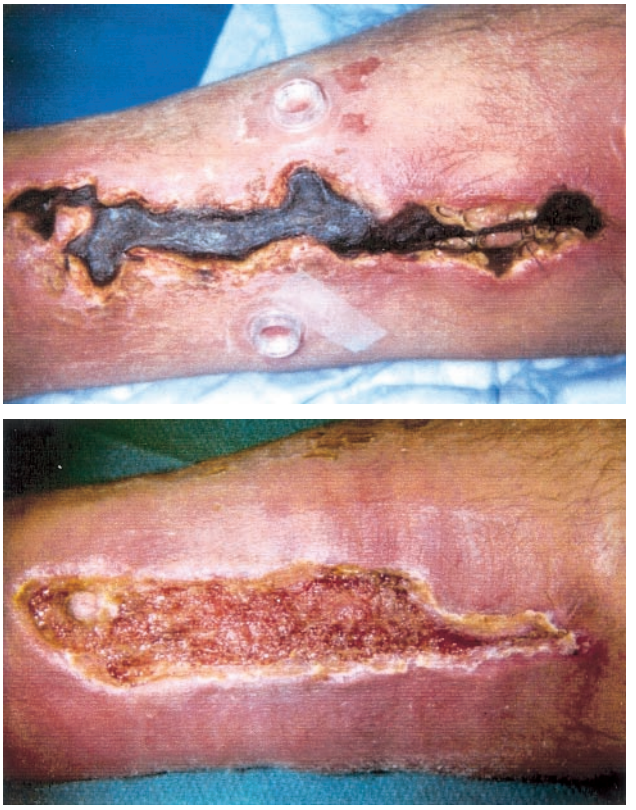

Fig. 2. (**a**) Patient #1, calciphylaxis of calf, July 1998. $P_{tc}O_2$ probes are seen above and below the wound. (**b**) Wound healing, November 1998.

Table 2. Outcomes

Patient	Diagnosis to treatment (months)	Number of HBO_2 treatments	Outcome
1	2	25	Recovered. Patient then died 9 months after resolution of calciphylaxis with a draining fistula of the lower abdomen
2	2	28	Recovered. Patient had severe angina and discontinued dialysis 29 months later
3	2	30	Left leg improved, right leg ulcer progressed. Requested withdrawal of care, patient died
4	.5	35	Requested withdrawal of care, patient died
5	.5	27	Calciphylaxis wound did not improve. Affected leg amputated. Patient died 4 months later of a myocardial infarction

HBO_2, hyperbaric oxygen.

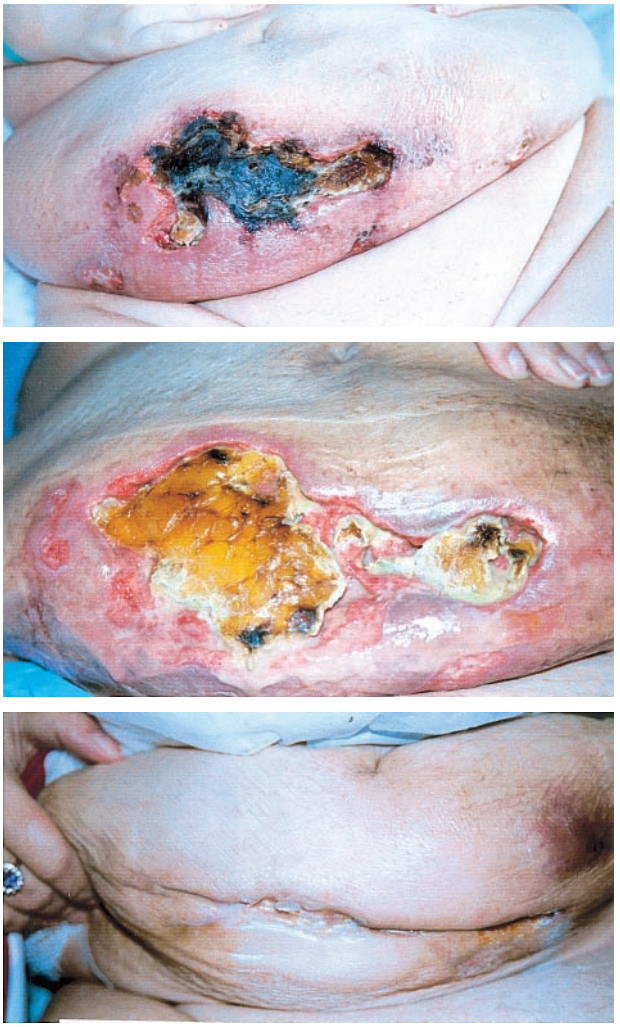

Fig. 3. (**a**) Patient #2, necrotic area of calciphylaxis on abdominal pannus, April 1997. (**b**) Granulation and healing, May 1997. (**c**) Area healed, November 1997.

levels for tissue healing (1 mmHg on room air and 18 mmHg on 100% O_2 normobaric). Diabetes mellitus and severe peripheral vascular disease were comorbid conditions in both patients. Both of these patients died from the complications of sepsis. The third patient who did not respond to HBO_2 (#5) had a large circumferential lesion on one calf. After the course of treatment with HBO_2, the wound had not improved sufficiently, and the patient required a below-knee amputation of the affected leg. Of note, this patient was diabetic, and had poor glucose control during the course of therapy, with serum glucose levels consistently above 350 mg/dl. Furthermore, in this patient transcutaneous oximetry did not demonstrate improved tissue oxygenation at the wound sites, which remained severely hypoxic (12 mmHg) on both room air and 100% O_2 normobaric.

Two patients receiving HBO_2 experienced claustrophobia. However, potential complications such as barotrauma, seizures, or visual refractive changes were not observed [18].

Discussion

In this retrospective study, five patients with biopsy-proven calciphylaxis were treated with HBO_2. Two patients had eventual complete resolution of their calciphylaxis wounds. These two patients both showed improvement in wound area $P_{tc}O_2$ with administration of 100% oxygen (Table 2) with measurements taken at normobaric and hyperbaric pressures respectively. In contrast, for two of the patients who did not improve with HBO_2, $P_{tc}O_2$ was measured and did not increase above 30 mmHg, a level associated with wound healing [14]. These measurements, however, were taken at normobaric pressures; the $P_{tc}O_2$ levels while these patients were in the hyperbaric chamber were not measured. Accordingly, it is uncertain whether HBO_2 therapy was associated with improved tissue $P_{tc}O_2$ levels in these cases.

Previous studies of calciphylaxis [1,11,19] indicate an unfavorable prognosis when the location of the skin lesions is proximal (26% survival) compared to distal (75% survival). One of the patients (#1) who recovered with HBO_2 therapy was in a favourable prognostic group, with only distal leg lesions, while the other (patient #2) had a large lesion of the abdominal pannus which completely healed with HBO_2 therapy (Figures 2 and 3).

Of the three patients who received HBO_2 therapy but did not improve (#3, #4, and #5), all had severe peripheral vascular disease and diabetes, and two had proximal lesions. In this regard, it is possible that severe diabetic microvascular disease may limit the delivery of oxygenated blood to the wound site and impair healing. This is reflected in the poor $P_{tc}O_2$ levels measured in two of these patients.

In our study, calciphylaxis occurred in patients with similar characteristics to those described in previous studies. Patients with ESRD and calciphylaxis tend to be relatively young (48 ± 16 years) [6,20], obese, female, and have low levels of serum albumin [1,3,21,22]. An increased incidence of calciphylaxis with the use of warfarin has also been noted [3]. For patients on haemodialysis, the length of time on treatment prior to development of calciphylaxis has been reported to range from 33 months [1] to 80 months [2]. Indeed, our five patients were fairly typical of patients described in the literature, with an average age of 50.8 years, and four were female, two were on warfarin therapy, all five had low serum albumin levels, and four were obese.

Elevations in serum PTH level have been noted in many cases of calciphylaxis [3,7,20]. However, the development of calciphylaxis in patients with normal levels of PTH [12,21,23,24] or after parathyroidectomy [2] is also commonly reported. In our study, none of the patients had uncontrolled hyperparathyroidism, and the majority (four of five) were being treated for secondary hyperparathyroidism with $CaCO_3$ and/or vitamin D to lower the serum PTH to 2–3 times normal. The role of these medications in calciphylaxis is controversial. It has been suggested that calciphylaxis

may be delayed or avoided with the prevention of secondary hyperparathyroidism through medical therapy [2]. On the other hand, $CaCO_3$ therapy has been reported as a risk factor for developing calciphylaxis in ESRD [23,25], perhaps due to its potential to cause hypercalcaemia [7]. Vitamin D has been used to suppress PTH in the treatment of calciphylaxis [26], although there are no controlled trials to support or refute its use as an effective treatment.

Most agree that parathyroidectomy should be considered as therapy for calciphylaxis when severe hyperparathyroidism is present [2,5–7]. However, in the presence of mild elevations of PTH, or with normal PTH levels, no clear benefit of parathyroidectomy has been identified [8,27].

Three of our patients (#2, #3, and #5) were vulnerable to desaturation while breathing room air. It is of note that previous autopsy studies show that 60% of chronic dialysis patients, as well as those with calciphylaxis, have extensive pulmonary calcification [7,28]. It is possible that patients with calciphylaxis are more vulnerable to develop systemic hypoxia, worsening their predisposition to wound hypoxia. If HBO_2 is not available or possible, it is conceivable that patients with calciphylaxis may benefit from continuous supplemental oxygen.

In conclusion, two of five patients in our study demonstrated complete healing of their calciphylaxis wounds when treated with HBO_2. As in our study, most patients with calciphylaxis do not have uncontrolled hyperparathyroidism, leaving them with few therapeutic options. Our data suggest that HBO_2 is safe and has a role in the treatment of calciphylaxis.

Acknowledgements. The authors would like to thank Dr Susan Robertson, Associate Professor, Department of Anatomic Pathology and Dr John Veinot, Associate Professor, Department of Anatomic Pathology, University of Ottawa for their assistance with histologic analysis of tissues. This study was supported by funds from the Kidney Research Centre, Ottawa Health Research Institute, University of Ottawa.

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Received for publication: 10.1.01
Accepted in revised form: 11.6.01