Bubbles in the skin microcirculation underlying *cutis marmorata* in decompression sickness: Preliminary observations

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Abstract
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Introduction: The cutaneous form of decompression sickness (DCS) known as *cutis marmorata* is a frequent clinical presentation. Beyond a general acceptance that bubbles formed from dissolved inert gas are the primary vector of injury, there has been debate about pathophysiology. Hypotheses include: 1) local formation of bubbles in the skin or its blood vessels; 2) arterialisation of venous bubbles across a right to left shunt (RLS) with local amplification in bubble size after reaching supersaturated skin via the arterial circulation; and 3) passage of arterialised venous bubbles to the cerebral circulation with stimulation of a sympathetically mediated vasomotor response.
Methods: Four divers exhibiting *cutis marmorata* had the underlying tissue examined with ultrasound 4–5.5 hours after appearance of the rash. All subsequently underwent transthoracic echocardiography with bubble contrast to check for a RLS.
Results: In all cases numerous small bubbles were seen moving within the skin microvasculature. No bubbles were seen in adjacent areas of normal skin. All four divers had a large RLS.
Conclusion: This is the first report of bubbles in skin affected by *cutis marmorata* after diving. The finding is most compatible with pathophysiological hypotheses one and two above. The use of ultrasound will facilitate further study of this form of DCS.

Introduction

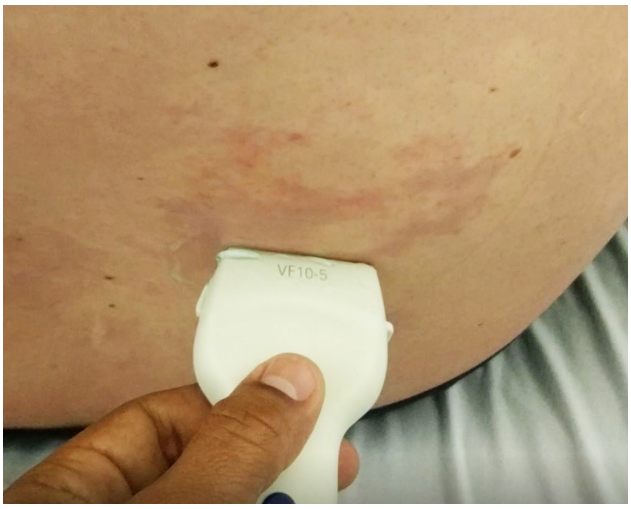
Decompression sickness (DCS) may occur in divers, aviators, astronauts or personnel decompressing from work under hyperbaric conditions. It is primarily caused by the formation of bubbles from dissolved inert gas during or after decompression.[1] These bubbles may form in tissues or in blood passing through them. The resulting venous bubbles are typically removed from circulation in the lung capillary bed and are usually asymptomatic.[1] However, they may cross to the arterial circulation via a right to left shunt (RLS) such as a persistent (patent) foramen ovale (PFO) or a pulmonary shunt, and may then enter the microcirculation of vulnerable target tissues where diffusion of supersaturated inert gas from surrounding tissue could cause them to grow.[2,3] Vascular bubbles may cause endothelial injury which can incite platelet aggregation, activation of leukocytes and fibrin deposition leading to reduced flow, greater vascular permeability and tissue oedema that exacerbates ischaemia. Cytokine release, complement activation and microparticle production are part of this inflammatory milieu and may contribute to tissue injury.[4,5] The variability in the activation of inflammatory processes could contribute to the differences between individuals in susceptibility to DCS as well as the highly variable clinical presentations which can range from a mild syndrome to a life threatening condition.[5]

CUTIS MARMORATA

One of the signs of DCS is a rash known as *cutis marmorata*. This presents with a mottled, livedoid appearance that is typically distributed 'centrally' over tissues with significant amounts of subcutaneous fat;[6] for example on the chest, back, abdomen, breasts, buttocks, upper arm and thigh areas. This may be accompanied by pruritus, pain or burning. The rash may appear in isolation or combined with other DCS manifestations, such as neurological symptoms. In the experience of the present authors, it is a common finding in patients with haemodynamic shock associated with DCS.

In the absence of co-existing serious symptoms or signs a rash is, of itself, considered a 'mild' manifestation of DCS.[7] However the 'mild' characterisation must be applied cautiously. There is a strong association between appearance

Figure 1
Cutis marmorata rash on the lower back with ultrasound probe in place



of *cutis marmorata* after diving and the presence of a large right to left shunt such as a PFO whose significance was explained above.[2] Other more serious manifestations such as cerebral, spinal and vestibulocochlear symptoms are also associated with a PFO,[8] and care must be taken to look for these problems when a diver presents with *cutis marmorata*.

PATHOPHYSIOLOGY

As with most manifestations of DCS, beyond the presumed involvement of bubbles as the primary vectors of injury, there has been uncertainty and controversy surrounding the underlying pathophysiology of *cutis marmorata*. The histopathological findings were described in a porcine model of DCS.[9] The main changes observed were an increase in skin thickness, elevation in nitric oxide, congestion, and deposits of red blood cells that clogged the dermal capillaries. Vascular dilation, haemorrhage and neutrophil infiltrates were also reported. However, that study did not elucidate the mechanisms inciting these changes. Three principle pathophysiological theories have been proposed.

Hypothesis one. Bubbles could form locally in the skin; either in the extravascular tissue, or within the subcutaneous micro-vasculature.[8] These bubbles could then produce symptoms through physical, prothrombotic and inflammatory processes alluded to above. A weakness of this theory is that bubbles have not previously been demonstrated in skin exhibiting *cutis marmorata*.

Hypothesis two. The association between a large PFO and *cutis marmorata* strongly implicates venous inert gas bubbles crossing into the arterial circulation as vectors of injury.[2] After arriving in the skin these bubbles could grow through inward diffusion of locally supersaturated inert gas; a process Wilmshurst refers to as "peripheral amplification".[8] Once again, they could then produce symptoms through physical, prothrombotic and pro-inflammatory processes. As above, a weakness of this theory is that bubbles have not previously been demonstrated in the micro-vessels underlying skin exhibiting *cutis marmorata*. Moreover, in a recent study in a porcine model of *cutis marmorata* echocardiographic monitoring of the pigs showed no arterial bubbles despite the development of florid skin lesions.[10] The latter observation could be interpreted as supportive of hypothesis one.

Hypothesis three. It has been suggested that the association of *cutis marmorata* with a large PFO may be alternatively explained by passage of arterialised venous bubbles to the cerebral circulation. These bubbles may elicit release of neuropeptides[11] or alter sympathetic outflow activity[12] which could provoke a livedoid rash peripherally through vasomotor or pro-inflammatory changes. This 'central mediation' hypothesis draws heavily on the appearance of *cutis marmorata*-like rashes in non-dived pigs subjected to cerebral arterial gas embolism,[11] but it has several crucial weaknesses.[6] In particular, the dose of cerebral arterial air employed the pig study[11] is of doubtful relevance to DCS. It resulted in the death of some pigs and would likely have produced profound neurological injury had the survivors been allowed to emerge from anaesthesia, yet divers with *cutis marmorata* frequently have no neurological manifestations. Moreover, Wilmshurst also points out that patients undergoing PFO testing with bubble contrast never develop a rash even when the test is strongly positive and large showers of small bubbles enter the arterial circulation,[6] despite the fact that cerebral symptoms are sometimes reported in this setting.[13,14]

There is no clear consensus on which of these mechanistic hypotheses is pre-eminent although the association between *cutis marmorata* and PFO is compelling. It is plausible that all could be relevant under certain circumstances. We report here an incidental clinical observation of substantial relevance to the first two hypotheses.

Clinical observations

Observations were made on four DCS cases exhibiting *cutis marmorata* and treated at Cozumel, México. All patients gave permission for relevant clinical data to be reported.

Four divers presenting with *cutis marmorata* underwent ultrasound examination directly over the involved skin using a Siemens Acuson x300 2D ultrasound machine (Siemens, Fishers, USA) coupled with a linear 4.0–11.4 MHz transducer with examination depth set at 35 mm (see Figure 1). The examination took place between 4–5.5 h after finishing diving, and between 2–4.5 h after appearance of the rash. The examination was limited to a short period (< 10 minutes) so as not to delay recompression. In all cases, moving bubbles were detected in underlying arterioles and venules as well as interconnecting vessels and

Figure 2
Two screen shots from an ultrasound video loop showing the identical location beneath a cutis marmorata rash in DCS. In A, the arrow indicates a small cylindrical bubble. In B, the arrow indicates a hypoechoic void in the micro-vessel immediately after the bubble had passed through

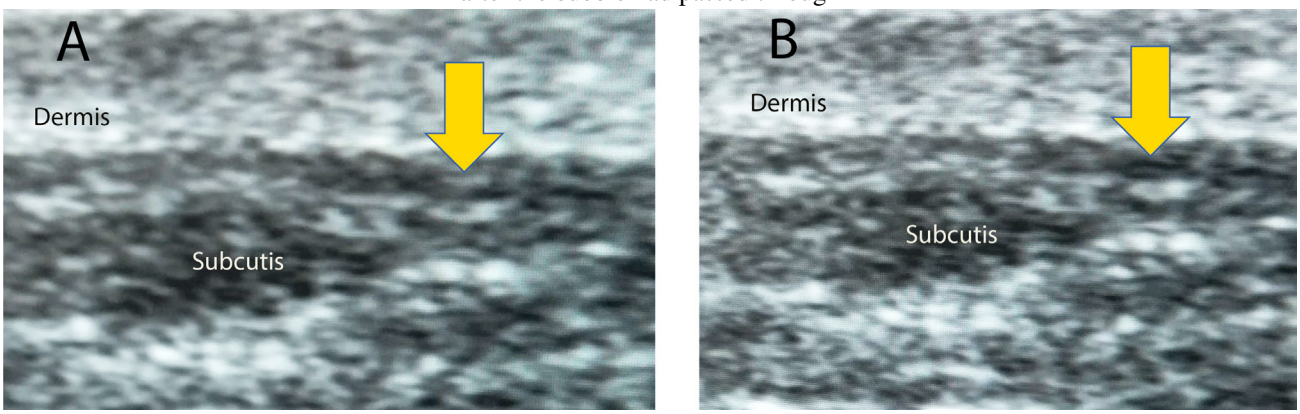


Table 1
Diving and clinical data for the four reported cases. Durations reported in the dive profile are total dive times and depths are maximum depths. All dives were compliant with the divers' dive computer recommendations. BMI = body mass index; DCS = decompression sickness; M = male; F = female; msw = metres' seawater depth; SI = surface interval

Case	Age	Sex	BMI	Dive profile	Symptoms other than *cutis marmorata*	Scan latency (hours)	Treatment
1	58	M	33	24 msw – 70 min; 50 min SI 18 msw – 78 min	Spinal DCS (decreased strength both legs, tingling, paresthesias)	4.0	1 x Table 6 6 x Table 9
2	51	M	44	27 msw – 68 min; 60 min SI 24 msw – 60 min; 90 min SI 21 msw – 56 min	Cerebral DCS (confusion, incoherence) Constitutional symptoms (fatigue)	5.0	2 x Table 6 1 x Table 5
3	42	M	40	43 msw – 43min; 60 min SI 19 msw – 60 min	Vestibular DCS	5.0	2 x Table 6 1 x Table 5
4	38	F	31	26 msw – 40 min; 60 SI 16 msw – 53 min; 60 SI 14 msw – 47 min	Vestibular DCS	5.5	2 x Table 6 1 x Table 5

capillaries. No attempt was made to quantify or measure the bubbles, but some were large enough to have formed cylindrical shapes in these micro-vessels (see Figure 2), and it can be confidently assumed that the bubbles were therefore large enough to be interacting with the vascular endothelium. In all cases there was tissue oedema apparent under the rash which can be the result of extravasation of fluids following physical or inflammatory damage to the endothelium. A short segment of video illustrating some of these observations can be found by following the link https://www.dhmjournal.com/index.php?option=com_content&view=article&id=70. Examination of normal skin adjacent to areas of *cutis marmorata* revealed no bubbles large enough to be seen using this ultrasound technology. It is germane to note that this report is not selective. No divers with *cutis marmorata* have been examined with ultrasound who did not exhibit bubbles in the subcutaneous circulation underlying the rash.

Consistent with the associations described earlier, all of these cases exhibited neurological manifestations in addition to the rash (two vestibular, one cerebral and one spinal). All were recompressed on a US Navy Treatment Table 6 as the initial intervention, and had variable numbers of follow-up treatments (maximum seven) (see Table 1). In all cases the rash resolved completely after two (two cases) or three (two cases) recompressions. It is notable that all four divers subsequently underwent transthoracic echocardiography using bubble contrast to test for a RLS; all were positive (two characterised as large, and two as small). All four divers had a body mass index (BMI) between 31 and 44.

Discussion

We believe this is the first observation of bubbles present in the subcutaneous tissues beneath a *cutis marmorata* rash in DCS. The finding must be interpreted cautiously in relation to the above mechanistic hypotheses, though it does address the criticism in relation to hypotheses one and two that local bubbles have never been demonstrated in *cutis marmorata*. The mere presence of bubbles does not prove a causative role, but it is a highly relevant observation.

We cannot be sure whether these bubbles originated through local formation or represent small venous bubbles that have crossed a RLS. The fact that all four subjects exhibited an elevated BMI and therefore had greater truncal subcutaneous fat in which nitrogen is highly soluble plausibly supports a local formation mechanism. However, the finding of a RLS in all four divers is also consistent with them having crossed a RLS from the venous circulation. These observations raise the question as to why adjacent skin unaffected by rash would not exhibit subcutaneous vascular bubbles; fat content should be similar, and any bubbles crossing a RLS should distribute widely and approximately uniformly. One possible explanation in relation to bubbles crossing a RLS holds that they might become larger and more visible in those areas of skin with relatively greater degrees of tissue gas supersaturation, but this is speculation and once again, it is not immediately obvious why this would be different in adjacent areas of skin.

This incidental finding is a preliminary observation. It is reported here in the absence of a more systematic approach to its investigation because of its potential importance to the pathophysiological hypotheses discussed above, and in the expectation that it may provide motivation for clinicians with access to the right equipment to move forward with further evaluations. Future work could include a more careful evaluation of bubbles beneath the rash versus normal surrounding tissue, an evaluation of subcutaneous bubble activity correlated against the appearance of the rash (for example, during its resolution), and examination for the presence of bubbles in a wider group of divers with *cutis marmorata* to establish whether they appear in divers without a RLS. Another important future step would be to simultaneously perform echocardiography and observation of bubble activity beneath a *cutis marmorata* rash to see if the presence of bubbles in the skin corresponds with bubbles appearing in the left heart (consistent with hypothesis two). The skin is arguably one of the most accessible of the DCS target tissues for study, and ultrasound examination would appear to be a potentially useful tool in studying pathophysiology. The presence of bubbles and the inflammatory reaction that they generate after their vascular passage might provide insight into how other vulnerable tissues such as the inner ear, spinal cord or brain behave after the insult caused by bubbles.

Conclusions

This report confirms that mobile vascular bubbles are present in the subcutaneous microcirculation in tissue underlying a *cutis marmorata* rash. A causative role cannot be confidently inferred, but the finding of bubbles strengthens the hypotheses that bubbles formed locally or distributing to the skin after crossing a RLS and undergoing peripheral amplification may be the primary agents of harm in *cutis marmorata*.

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Conflicts of interest and funding

Professor Mitchell is the Editor of *Diving and Hyperbaric Medicine* Journal and had no role in managing the review process or the decision to accept this manuscript. These matters were managed by the European (deputy) Editor, Dr Lesley Blogg. There were no other conflicts of interest.

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