Case Report

Laser Doppler Imaging: Usefulness in Chronic Pain Medicine

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Sympathetic nervous system dysfunction is thought to be a factor in neuropathic pain conditions such as Complex Regional Pain Syndrome and in vascular conditions such as Raynaud's phenomenon. Laser Doppler fluxmetry has been used as a fast non-invasive method to quantify changes in skin capillary blood flow which reflect activation of sympathetically mediated vasoconstriction of the arterioles that supply the capillaries.

Studies of dynamic change of skin capillary blood flow with sympathetic activation such as cold or inspiratory gasp have generally used single point laser Doppler systems where the probe is in contact with the skin. The results are a single line tracing representing the capillary flow at a single point on the skin a few millimeters in diameter.

Laser Doppler imaging (moorLDI laser Doppler imager, Moor Instruments Ltd.) allows for non-contact recording of skin blood flow of an area as large as 50 centimeters square with a resolution of 256 by 256 pixels and 4 milliseconds per pixel. Most work with laser Doppler imaging has studied changes that occur between successive scans. We have found it useful to look at changes that occur during a scan. In this way we obtain data that is comparable to the time resolution of single point laser Doppler methods, but with the larger spatial information that is available with laser Doppler imaging.

We present a small series of case reports in which inspiratory gasp during laser Doppler imaging was able to provide quick, useful and unequivocal clinical information regarding the status of regional bilateral skin capillary response to sympathetic activation. This may be useful for distinguishing sympathetically mediated from sympathetically independent pain. We believe the methods described may provide the basis for future quantitative studies similar to those that use single point laser Doppler methods.

Key words: Laser doppler, laser Doppler imaging, sympathetically maintained pain, Raynaud's phenomen, complex regional pain syndrome

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Chronic neuropathic pain conditions such as Complex Regional Pain Syndrome (CRPS) show signs of involvement of the sympathetic nervous system. There may be evidence of vasodilatation, vasoconstriction, skin color changes, skin temperature asymmetries, hyperhidrosis or hypohidrosis (1). The degree to which the sympathetic nervous system is involved in the cause or maintenance of chronic neuropathic pain remains controversial (2). Clinical experience has shown that there are two subsets of CRPS patients, those who respond favorably to selective sympathetic blockade and those who show unfavorable or no response to these blocks (3). Patients with favorable pain response to sympatholytic treatment are said to have the symptom of "sympathetically maintained pain" and those without this symptom are said to have "sympathetically independent pain" (4).

Many patients who demonstrated a positive response to regional sympathetic blocks were surgically sympathectomized in the painful region in the hope of providing permanent relief. Unfortunately, in some cases surgical sympathectomy does not result in permanent relief of pain, especially in patients with longstanding symptoms prior to sympathectomy (5). The reasons for failure may be because the sympathectomy was incomplete, there was re-growth of fibers with time, or the symptoms have become sympathetically independent. Postsympathectomy neuralgia might be the result of sensitization of peripheral receptors to circulating norepinephrine (6).

Blood flow to the skin capillaries is under the control of the sympathetic nervous system. In general, activation of the sympathetic nervous system causes constriction of the arterioles that feed the capillaries, resulting in decreased capillary flow. Skin capillary flow can effectively be measured using laser Doppler.

Laser Doppler uses a low power helium neon laser transmitted as a beam onto the skin. The light is scattered by moving blood cells in the outermost 0.5 to 1 mm depth of skin and is frequency shifted according to the Doppler effect, the average Doppler frequency shift being directly proportional to the average speed of the blood cells. The scattered light is photodetected and the photo-current signal electronically processed to produce a flux analog signal.

An inspiratory gasp, a sharp chest-expanding deep breath, has been shown to evoke a sympathetic response resulting in a transient drop in capillary blood flow. This was originally reported using a plethymographic method in which the volume of a finger or toe decreased measurably with deep inspiration causing chest wall expansion, and this response required intact sympathetic innervation (7). The transient decrease in capillary flow can be visualized using laser Doppler fluxmetry. A number of studies have examined skin vasoconstriction response to a variety of autonomic stimulating maneuvers using single point laser Doppler systems. In a study of control subjects it was found that inspiratory gasp and cold exposure were the most reliable in eliciting a skin vasoconstriction response (8).

While single point systems give good temporal resolution, the flux values can vary greatly with positioning of the probe. Changes in flux that accompany sympathetic activation might also vary greatly depending on the proximity of arterioles and venules to the probe location.

In laser Doppler imaging, the laser light is projected onto the skin from a distance and --with the use of a motor controlled mirror-- moves the beam in a precise raster pattern, line by line, from the lower left to the upper right of the area being scanned. A pixel by pixel pseudocolor image of flux measurements is produced.

This study was undertaken to determine if laser Doppler imaging could be used with sympathetic activating stimuli such as an inspiratory gasp or cold presser for routine diagnostic purposes. We report the results of a small patient series in which laser Doppler imaging proved useful in clinical practice.

Methods

Laser doppler imaging was performed in a dedicated room, temperature 24-26° C, with a moorLDI laser Doppler imager (Moor Instruments Ltd., Millwey, Axminster, Devon EX13 5HU, England). All images were collected at a setting of 4 milliseconds per pixel and most were at a maximum resolution of 256 x 256 pixels. The total time required for an image at these settings is approximately 4.5 minutes. All patients wore protective eyewear during the imaging process.

The laser Doppler imaging was performed with the subject in a reclined position with feet and hands at heart level. The hands were placed on a dark pillow on the patient's lap. Although each image can take as long as 4.5 minutes to collect, none of the subjects complained of discomfort while maintaining the hands on the pillow in the palms up position. For the plantar foot images, the subject merely kept the feet still while in the reclined position. Baseline images were obtained after an acclimation time of at least 10 minutes. Immediately following this, a second image was collected. In this image, the patient was instructed to take a deep inspiratory gasp and hold for 10 seconds at various times during the collection of the image.

Thresholds for cool and warm sensation, and cold and heat pain were obtained bilaterally on the thenar with the TSA-II Neuro Sensory Analyzer (Medoc Advanced Medical Systems U.S., Durham, NC). A ramping algorithm was used for all cool and warm detection thresholds. The baseline temperature was 32°C with a +1°C per second change for warming, or -1°C per second change for cooling. Subjects were instructed to push the response button, which recorded the temperature and reset the thermode back to baseline, as soon as they detected a change in temperature. For heat or cold pain determinations subjects were instructed to push the response button only if the sensation changed from cold or hot to one of pain.

Results

A typical baseline image of the palms of a control subject is shown (Fig. 1A) and a typical normal response to repeated inspiratory gasps (Fig. 1C). Since the laser beam moves in a raster pattern from the fingertips to the wrists, the reduction in capillary flow produced by inspiratory gasp is seen as a darker blue color in the pseudo-color image. Since the laser beam is moving relatively slowly, about 1.65 seconds for each horizontal line, only that part of the fingers or palms being

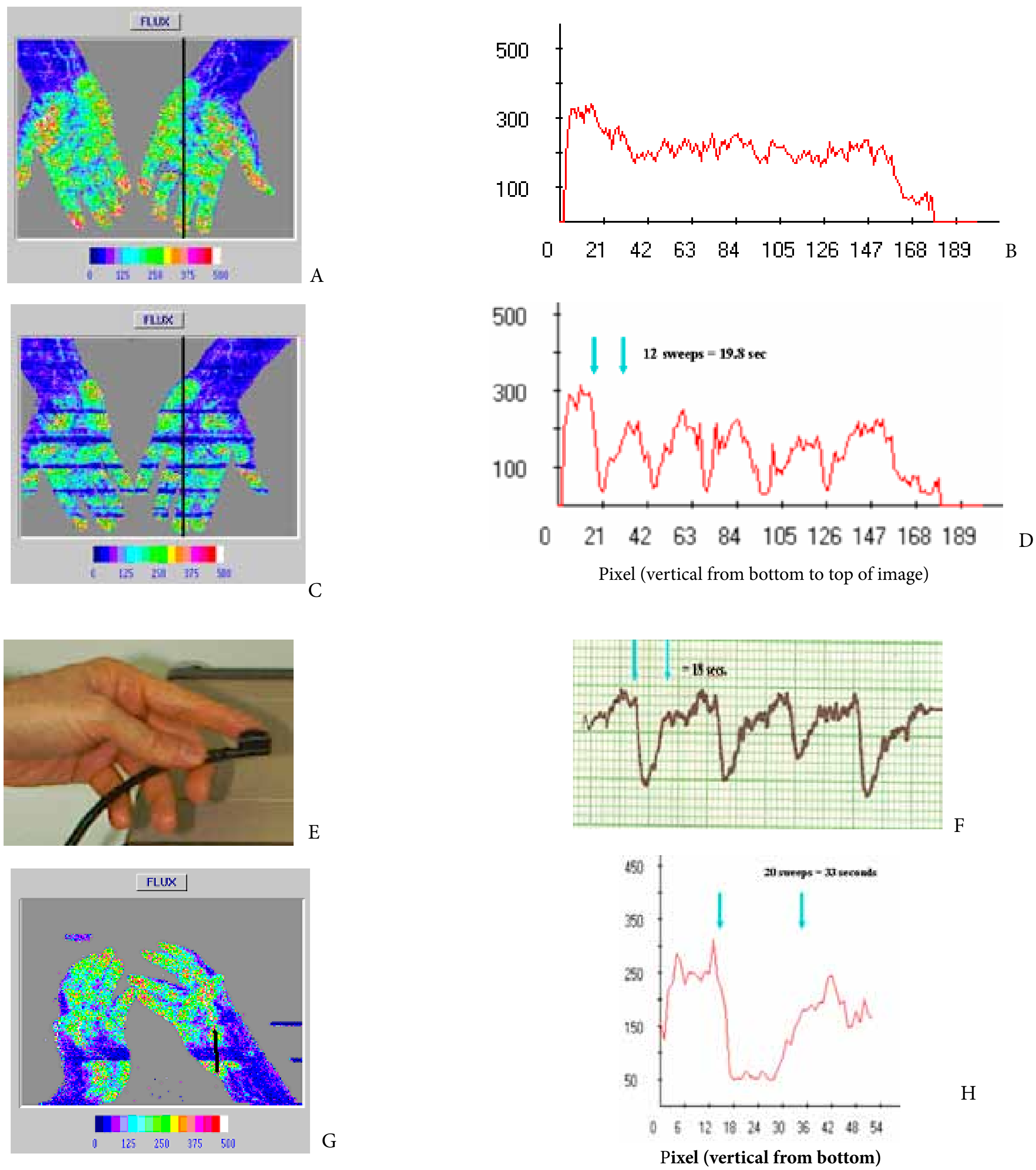

Fig. 1. *Laser Doppler images of control subject. (a) baseline; (b) flux values along 10 pixel wide line shown; (c) control with inspiratory gasps; (d) flux values along 10 pixel wide line shown; (e,f) single point laser Doppler of digit 2 with inspiratory gasps; (g) example of exaggerated inspiratory gasp response; (h) flux values along 10 pixel wide line shown.*

scanned during the transient drop in capillary flow, lasting about 15-20 seconds, displays this reduction. This can be seen clearly when the flux values from the bottom to the top of the image along a 10 pixel wide vertical line is shown (Fig. 1D). The horizontal scale for this graph is the scan line number. Since each scan line takes 1.65 seconds to complete, an estimate of the time between pixels on successive lines can be calculated. For comparison a representative tracing from a single point contact laser Doppler system (Laserflo blood perfusion monitor, TSI Inc., St. Paul, MN) of the index finger with repeated inspiratory gasps of the same control subject is also shown (Fig. 1F). The horizontal scale in this tracing is time with each vertical line of the chart recording being equal to 3 seconds.

An example of a laser Doppler image of a prolonged vasoconstriction response to inspiratory gasp is shown (Fig. 1G). In our experience this type of response is rarely seen and might be due to medication side effects, as has been described previously for single point laser Doppler inspiratory gasp evoked vasoconstriction response in amytryptyline treated patients (9).

Patient 1 was a 60-year-old woman with a long history of CRPS-I following an accident resulting in severe pain in her left arm and hand. Six years prior to laser Doppler imaging, she had a left thoracoscopic sympathectomy. She reported little or no relief following the procedure, and the painful condition progressed. At the time of laser Doppler testing she displayed normal thermal detection thresholds and cold hyperalgesia bilaterally, which was worse on the left, as well as slight heat hyperalgesia on the left hand compared to the right (Table 1).

The laser Doppler image at baseline shows that capillary flow was initially lower in the left hand (Fig. 2A). This could be interpreted as evidence of a chronic up-regulation of noradrenergic receptors following sympathectomy (6). The image in which the patient performed inspiratory gasps (Fig. 2B) displays bilateral reduction of capillary flow with the inspiratory gasps. This would indicate the presence of functional sympathetic innervation to both hands, the normal right hand and the symptomatic and sympathectomized sided left hand.

Patient 2 was a 46-year-old man with a 10-year history of CRPS-I in his left leg, which started following a severe knee injury. Ten years prior to laser Doppler imaging, the patient had a left lumbar sympathectomy. He reported some relief following the procedure, but with time the painful condition progressed. The laser Doppler image at baseline shows high and symmetrical baseline capillary flow in the bottom of the feet (Fig. 2C). The image in which the patient performed inspiratory gasps revealed robust sympathetic responses on the bottom of the right foot, but not on the affected, painful and sympathectomized sided left foot (Fig. 2D). This would indicate the absence of normal sympathetic vasoconstriction in the left lower extremity.

Patient 3 was a 56-year-old man with chronic pain in his upper extremities and suspected Raynaud's syndrome, since along with left sided neck and arm pain he reported that the fingers of both hands became painful, stiff and numb when they became cold. At the time of laser Doppler testing he displayed normal thermal detection thresholds in his hands and no evidence of cold or heat evoked thermal hyperalgesia (Table 1).

Table 1. *Thermal quantitative sensory results from patients described in results section. All results are reported as the change in degrees centigrade, at a rate of change of 1°C per second, from a baseline temperature of 32°C at which the patient detected (cool or warm detection) a thermal change, or when it became painful (cold or hot pain). The thermode (3cm x 3cm) was placed over the thenar eminence of the hand and secured with a Velcro strap.*

	Cool Detection (change from 32.0°C baseline)		**Warm Detection (change from 32.0°C baseline)**		**Cold Pain (change from 32.0°C baseline)**		**Hot Pain (change from 32.0°C baseline)**	
	Left	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
Patient 1 (thenar eminence)	-2.8	-2.6	+3.9	+2.7	-18.3	-12.2	+9.2	+12.2
Patient 3 (thenar eminence)	-2.6	-1.8	+2.5	+1.8	-32.0	-32.0	+13.	+13.7
Patient 4 (thenar eminence)	-1.2	-1.5	+1.5	+1.4	-23.5	-13.2	+11.4	+7.5

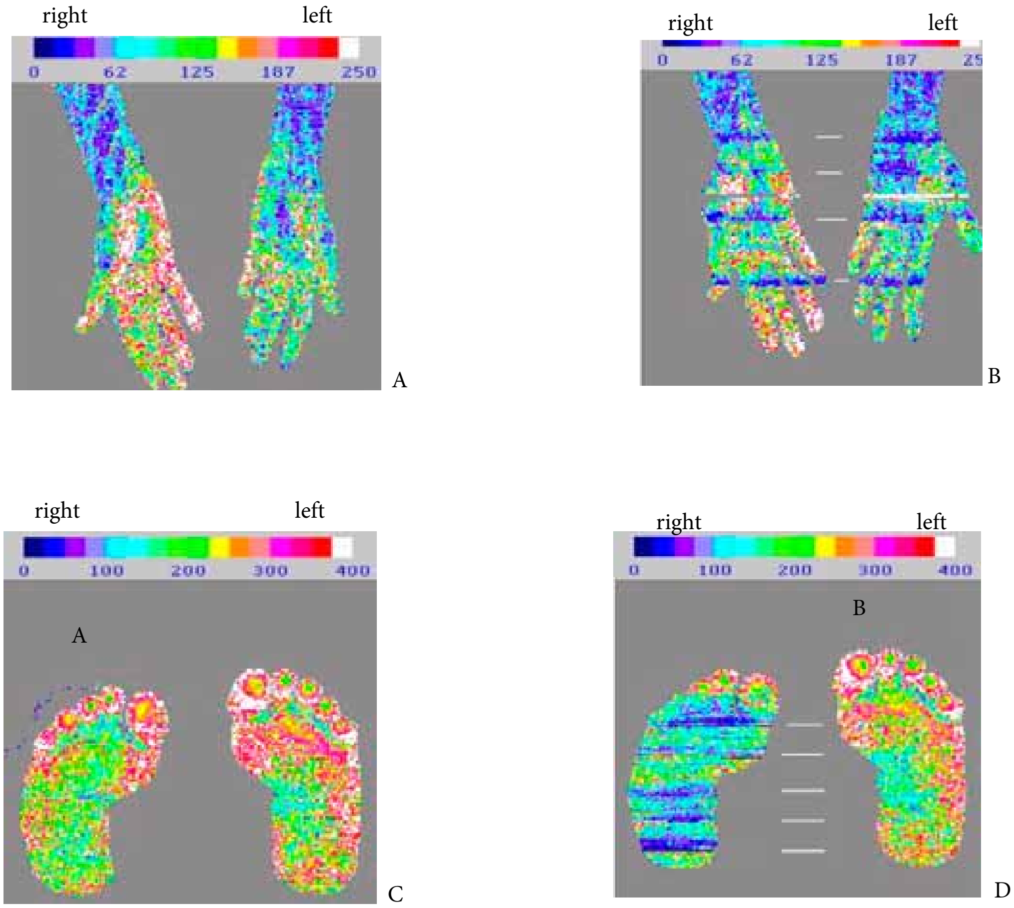

Fig. 2. *Laser Doppler images of baseline and inspiratory gasp evoked vasoconstriction in patients with prior sympathectomy. (a) baseline image of patient 1 (left upper sympathectomy, see text); (b) Patient 1 with inspiratory gasps; (c) baseline image of patient 2 (left lower sympathectomy, see text); (d) patient 2 with inspiratory gasps.*

Following the collection of a baseline image, which appeared normal and symmetrical (Fig. 3B), as well as an image with inspiratory gasps that indicated a normal response (image not shown), the patient immersed his hands up to the wrist crease in cold water (temperature 2-4oC). He was instructed to remove his hands when the pain became intolerable or when 30 seconds had elapsed. The patient reported some discomfort during and after the cold water immersion and removed his hands only after reaching the maximum time limit of 30 seconds. The hands were dabbed dry with a towel and then images were collected at timed intervals.

Laser Doppler images following immersion of the hands in cold water, show the expected response of someone with a Raynaud's condition. There is exaggerated and prolonged vasoconstriction following the cold exposure (Fig. B), compared to a control subject (Fig. 3A).

Patient 4 was a 50-year-old woman with chronic severe pain in her right upper extremity. She displayed normal thermal detection thresholds bilaterally, but had significant cold and heat evoked hyperalgesia in her right hand (Table 1). The patient complained of pain exacerbated by cold and Raynaud's syndrome was suspected. Following collection of a baseline image, which appeared normal and symmetrical (Fig. 3C), as well as an image with inspiratory gasps that indicated a normal response (Fig. 3D), the patient immersed her

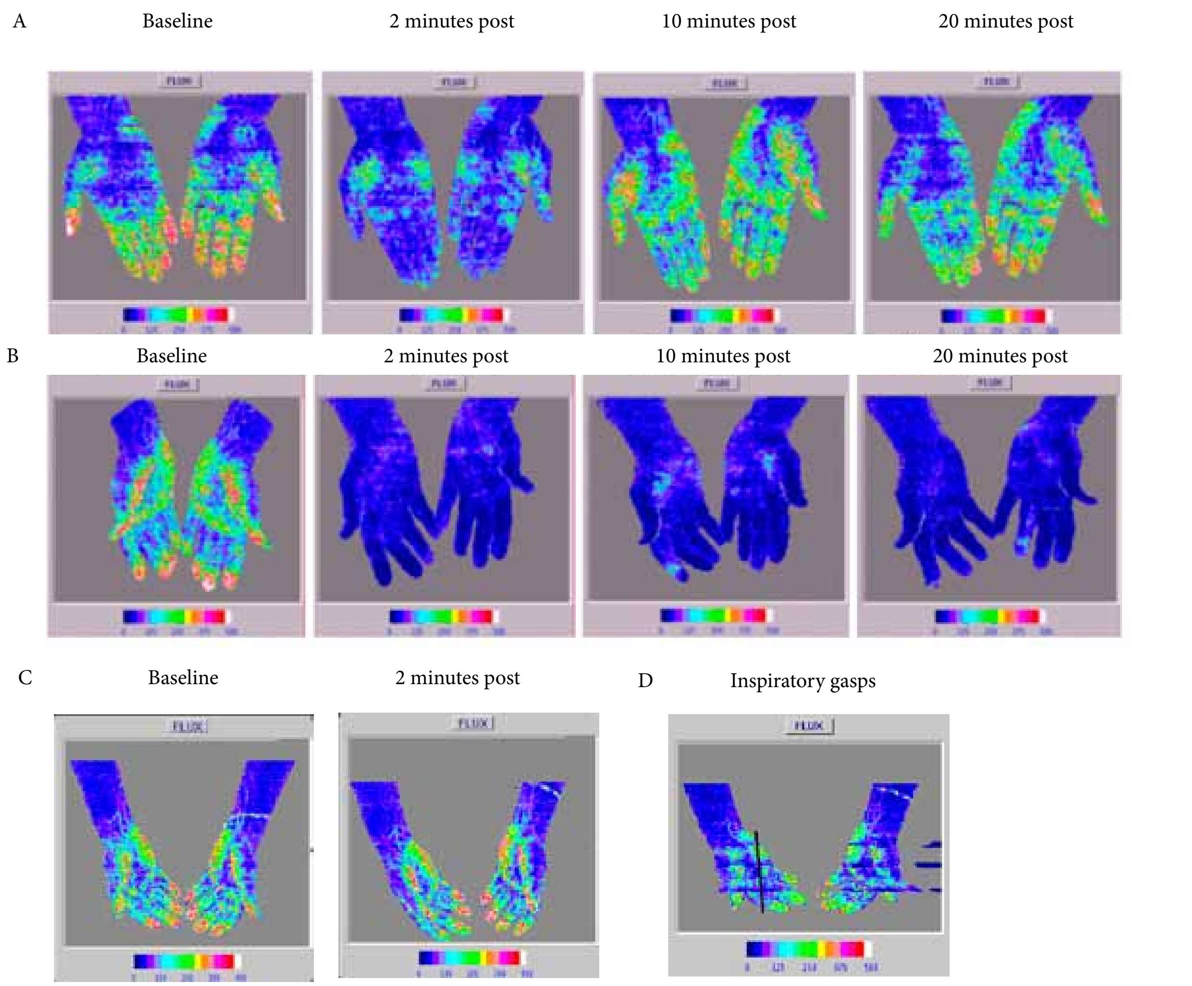

Fig. 3. *Laser Doppler images from control subject and patients with suspected Raynaud's syndrome. (a) control subject prior to and post bilateral cold water immersion of hands; (b) Patient 3(see text); (c) Patient 4 (see text); (d) Patient 4 (normal inspiratory gasp vasoconstriction response).*

hands up to the wrist crease in cold water (temperature 2-4oC) and was instructed to remove her hands when the pain became intolerable or when 30 seconds had elapsed. The patient reported severe pain during cold water immersion and removed her hands after only 11 seconds. The hands were dabbed dry with a towel and then images were collected at timed intervals.

In this patient severe pain on cold water immersion was not accompanied by vasoconstriction. The image taken only 2 minutes after removing the hands from the water shows no decrease in capillary blood flow to the painful hands (Fig. 3C). This, along with demonstration of normal vasoconstriction response to inspiratory gasp, makes it unlikely that painful vasoconstriction plays a major role in this patient's cold evoked hyperalgesia.

Discussion

Laser Doppler fluxmetry has been used in a number of studies to quantify sympathetically mediated skin vasoconstriction responses (10-13,21,22). Standard single point laser Doppler systems give excellent temporal resolution which can demonstrate vasomotion, the normal periodic changes in capillary blood flow resulting from pulsations, respiration and the normal fluctuations of sympathetic activity. A previous study by our group demonstrated loss or reduction of normal vasomotion in patients with CRPS compared to controls (14). The major shortcoming of single point laser Doppler systems is the lack of spatial resolution, as only one small pinpoint of skin is sampled, and there can be a great deal of position or movement artifact. Laser Doppler imaging allows for much greater spatial resolution, in that the skin from an entire region of the body can be sampled. The problem, however, is the lack of temporal resolution as each of the maximum 65536 (256 x 256) individual points that make up an image are sampled only once.

Laser Doppler imaging has been used to assess skin small fiber function by quantification of the neurogenic flare response to localized heating in diabetic neuropathy. Laser Doppler imaging was found to be superior to single point laser Doppler fluxmetry for this purpose since both the area as well as intensity of the evoked neurogenic flare could be quantified (20).

We have found that laser Doppler imaging can be useful for answering specific questions regarding peripheral sympathetic function in chronic pain patients. Although there are limitations, laser Doppler imaging can provide evidence to rule out localized sympathetic activation as a major contributor to cutaneous hyperalgesia. In a related laser Doppler imaging study, it was found that there was no change in skin blood blow with tactile stimulation in allodynic skin of patients with postherpetic neuralgia (15). We have previously used laser Doppler imaging to demonstrate lack of vascular occlusion or sympathetic hyperactivity contributing to sensory symptoms in patients with brachial plexus traction injury (16).

In addition to inspiratory gasp response, laser Doppler imaging following cold pressor might prove to be useful in the clinical workup of chronic pain patients with cold allodynia. Cold water immersion, when standardized, is simple to perform and has been shown to be a sensitive test for detecting analgesic effects of medications (17).

Laser Doppler imaging with inspiratory gasp can quickly and easily demonstrate the presence or absence of regional sympathetic vasoconstrictor function in the extremities. This can be especially useful in specific cases where sympatholysis has been performed or in cases of traumatic pain or complex regional pain syndrome. While simple presence or absence of vasoconstriction response is useful for clinical decision making, for research purposes it would be helpful if the vasoconstriction response could be quantified.

Quantification of inspiratory gasp evoked vasoconstriction response has been accomplished using single point laser Doppler methods and has been used to demonstrate a reduction of normal vasoconstriction response in early CRPS type I that appears to normalize with progression or remission of the disease (2,18,19). We are currently working to quantify skin vasoconstriction responses using laser Doppler imaging similar to what has been done with single point laser Doppler.

Thermal imaging, or thermography can provide spatial information about relative temperature differences which are often, but not always, related to surface skin blood flow. Laser Doppler imaging, however, provides the ability to visualize transient sympathetically mediated cutaneous vasoconstriction, which is something that thermal imaging cannot do. Laser Doppler imaging is very specialized and the equipment is expensive enough that it probably will not soon be part of routine clinical workup of chronic pain patients except possibly at specialized academic pain clinics.

This short report is presented not as a complete, quantitative study, but to provoke interest leading to possible improvements in methodology and quantification, as well as possible collaborations with others interested in the relationship of regional sympathetic function and chronic pain.

Acknowledgements

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References

1. Schwartzman RJ, Popescu A. Reflex sympathetic dystrophy. *Curr Rheumatol Rep* 2002; 4:165-169.
2. Gradl G, Schurmann M. Sympathetic dysfunction as a temporary phenomenon in acute posttraumatic CRPS I. *Clin Auton Res* 2005; 15:29-34.
3. Schwartzman R, Alexander G, Grothusen, J. Pathophysiology of complex regional pain syndrome. *Exp Rev Neurotherapeutics* 2006; 6:669-681.
4. Stengel M, Binder A, Baron R. Update on the diagnosis and management of complex regional pain syndromes. *Adv Pain Manage* 2007; 1:96-104.
5. Schwartzman RJ, Liu JE, Smullens SN, Hyslop T, Tahmoush AJ. Long-term outcome following sympathectomy for complex regional pain syndrome type 1 (RSD). *J Neurol Sci.* 1997; 150:149-152.
6. Pertovaara A. Noradrenergic pain modulation. *Prog Neurobiol* 2006; 80:53-83.
7. Bolton B, Carmichael EA, Sturup G. Vaso-constriction following deep inspiration. *J Physiol* 1936; 86:83-94.
8. Fegar J, Braune S. Measurement of skin vasoconstrictor response in healthy subjects. *Auton Neurosci.* 2005; 120:88-96.
9. Mueck-Weymann M, Rechlin T. Reflexes of the cutaneous microcirculation in amytryptyline and in fluoxetine treated patients. *Psychopharmacology* 1996; 124:241-244.
10. Birklein F, Riedl B, Neundorfer B, Handwerker HO. Sympathetic vasoconstrictor reflex pattern in patients with complex regional pain syndrome. *Pain* 1998; 75:93-100.
11. Mayrovitz HN, Groseclose EE. Inspiration-induced vascular responses in finger dorsum skin. *Microvascular Research* 2002; 63:227-232.
12. Mayrovitz HN, Groseclose EE. Neurovascular responses to sequential deep inspirations assessed via laser-Doppler perfusion changes in dorsal finger skin. *Clinical Physiology and Functional Imaging* 2002; 22:49-54.
13. Mueck-Weymann M, Rauh R. Do preceding vasoconstrictions influence the inspiratory gasp test? *Clinical Physiology and Functional Imaging* 2002; 22:206-209.
14. Bej, MD and Schwartzman, RJ: Abnormalities of cutaneous blood flow regulation in patients with reflex sympathetic dystrophy as measured by laser doppler fluxmetry. *Arch Neurol* 1991; 48:912-915.
15. Besson M, Brook P, Chizh BA, Pickering AE. Tactile allodynia in patients with postherpetic neuralgia: Lack of change in skin blood flow upon dynamic stimulation. *Pain* 2005; 117:154-161.
16. Schwartzman RJ, Grothusen JR: Brachial plexus traction injury: Quantification of Sensory Abnormalities. *Pain Med* 2008; 9:950-957.
17. Koltzenburg M, Pokorny R, Gasser UE, Richarz U. Differential sensitivity of three experimental pain models in detecting the analgesic effects of transdermal fentanyl and buprenorphine. *Pain* 2006; 126:165-174.
18. Schurmann M, Gradl G, Andress HJ, Furst H, Schildberg FW. Assessment of peripheral sympathetic nervous function for diagnosing early post-traumatic complex regional pain syndrome type I. *Pain* 1999; 80:149-159.
19. Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. *Brain* 2001; 124:587-599.
20. Krishnan STM, Rayman G. The LDIflare: A novel test of C-fiber function demonstrates early neuropathy in type 2 diabetes. *Diabetes Care* 2004; 27:2930-2933.
21. Baron R, Schattschneider J, Binder A, Siebrecht D, Wasner G. Relation between sympathetic vasoconstrictor activity and pain and hyperalgesia in complex regional pain syndromes: a case-control study. *Lancet* 2002; 359:1655-1660.
22. Lehtipalo S, Winso O, Koskinen LOD, Johansson G, Biber B. Cutaneous sympathetic vasoconstrictor reflexes for the evaluation of interscalene brachial plexus block. *Acta Anaesthesiol Scand* 2000; 44:946-952.