30 Years of Microvascular Monitoring

We are proud to highlight that this May marks the start of our 30th financial year in business for Moor Instruments. To celebrate that milestone, alongside other activities (such as our new temporary logo which you may have noticed!) we plan a series of short articles through the year to help document our history, achievements and the products and applications we have helped to create.

In this, the first article in the series, we will focus on our company history and the laser Doppler monitors we have offered from the start. Our grateful thanks goes to those customers who helped track down an example of each from our portfolio enabling us to recently commission a photo shoot, the results of which follow.

Moor Instruments was incorporated by Dr David Boggett (Dave to all). Dave is still chairman at Moor Instruments and takes a very keen interest in our technical innovations and product development.

Dr David Boggett – with a young Pete Jady (Sales and Marketing Manager).

One of the most common questions we are asked is "Why Moor"? The simple answer being that it is an abbreviation of Dave's property name, "Moorland Ridge" from where the fledgling company took its first steps originally in a shed, moving into the house and out again to an industrial unit in Axminster, where we are now headquartered in somewhat expanded premises.

Dave's interest in laser Doppler blood flow measurements started way before the birth of Moor as it was a research interest at Oxford Brookes University where Dave headed a small research team. It was there that prototypes were developed which collaborators around the UK felt were as good as anything else commercially available and encouraged him to start manufacturing more seriously. This ultimately resulted in a move away from academic life from Oxford to live in rural East Devon close to the Jurassic Coast.

MBF1– single channel monitor.

The company's first laser Doppler monitor was the MBF1 (Moor Blood Flow 1), which did not actually include a laser, an external source was used instead. The unit also had analogue outputs, enabling you to connect to a chart recorder (for those old enough to know what they are!) but also showed some forward thinking as this 30 year old monitor would interface happily with todays modern A-D data acquisition systems. The MBF1 was a solderers delight though – labour intensive in manufacture. As interest developed, it became obvious that more attention should be paid to easing manufacture.

MBF2 – single channel monitor.

To some extent, this was resolved with the MBF2 monitor. The MBF2 was the largest monitor we ever produced, because a Helium Neon tube laser was used internally.

MBF3D – dual channel monitor.

As more staff came on board, work could begin on the MBF3 series which featured a (world first) dual channel design to allow comparisons of blood flow at stimulated and control sites. With the take-off of commercial laser diodes commonly found in CD, DVD players in car and home, we could take advantage of the much more compact laser packages and added heating/ cooling circuitry to keep the lasers ultra-stable, (which is still our solution today). The monitor also featured a graphical display, inbuilt data memory and inbuilt colour plotter – again all features that were well ahead of their time. The additional freedom provided by advances in microprocessor design enabled cutting edge design and functionality. The MBF3 was one of the first real commercial successes of the company and really established us as a highly competitive supplier and gave confidence to recruit other staff to boost production, sales and marketing and to develop new systems. It was around this time too that plans were made to launch Moor Instruments properly in the USA, with the formation of Moor Instruments Inc in Delaware (East coast).

DRT4 – dual channel monitor with temperature measurement.

Whilst the basic offering of the MBF3D was strong (and would still compete today!) advances in hardware design meant the DRT4, next generation was inevitable. The DRT4 was based on the MBF3D but featured a wipe clean membrane panel intended more for clinical research and a direct printer interface. We also recognised that skin temperature was an important co-parameter to measure so were the first to produce a combined blood flow/ skin temperature probe.

moorLAB – server with additional satellite channels.

Not wanting to turn our back on the researchers who were interested more in a lower cost, stripped back version of the clinically oriented DRT4 (no graphical screen, no data memory), we followed up with the floLAB/ moorLAB multi channel monitor, enabling up to three channels to be added to the base Server unit. It was around this time we started to get involved with laser Doppler imaging too, funded by the success of the MBF3 and DRT4.

moorVMS-LDF – dual channel module.

We sold DRT4 and moorLAB alongside each other for a number of years before work started again on a direct replacement for both – taking advantage of digital signal processing to create the moorVMS range which we sell currently. Digital signal processing keeps the component count down and fewer parts leads to better reliability (reflected in the 5 year moorVMS-LDF warranty) with lower production costs (lower sale costs) and makes the system relatively compact.

moorVMS – modules from the moorVMS family.

Over recent years we have focussed on building up the range of modules within the moorVMS range, adding protocol modules to assess the response to heating and pressure cuff inflation.

We also added white light spectroscopy for superficial measurements of blood oxygenation in collaboration with researchers at the University of Remagen (also marking the launch of Moor Instruments GmbH - joining Moor Instruments Inc as a sister company). The most recent addition is moorVMS-NIRS for deeper measurement of oxygen – in the muscle and cerebral tissue for example.

moorVMS-NIRS – dual channel module.

Throughout, we have added options to standardise and automate the more common blood flow provocations, from transdermal drug delivery (MIC1, MIC1-e and MIC2), pressure cuff control (moorVMS-PRES) and tissue heating (SH01, SH02 and moorVMS-HEAT).

Alongside the hardware developments, we have maintained progress with software development to “glue” your choice of modules together according to your precise needs. Find out more at www.moor.co.uk and www.moorclinical.com.

There is no doubt that Moor was founded on blood flow monitoring and together with the other modalities we have offered, contributes significantly to our further growth and product development.

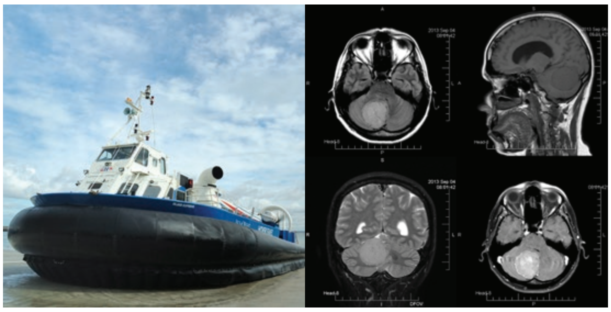
For the next article we will focus on blood flow imaging. If there are any questions about this article, or future articles, please do not hesitate to get in contact 30@moor.co.uk.

Burn Assessment and what links Moor Instruments and the hovercraft

As part of the celebration of our 30th year in business, we are producing a series of four articles to document key milestones in our history. The first article focussed on how laser Doppler monitoring was a founding product for our business and still plays a key role today (and can be found on our website). In this, the second article, we focus on how the accuracy of burn assessment has been improved by applying non-contact laser Doppler imaging technology to the benefit of patients and clinicians alike.

Newcastle and BTG

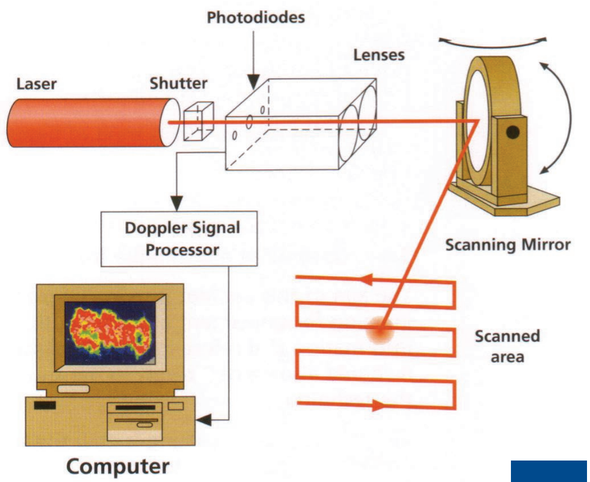
The history of Burn Assessment at Moor starts in 1996 when we were approached by Tim Essex and Philip Byrne of Newcastle University who had developed and patented a unique laser Doppler imaging technique to provide colour coded images of blood flow in the microvasculature. Although there was another commercially available system from Sweden (for which we were the UK distributor), the Newcastle system used a continuously moving beam which offered much faster, high resolution scans and critically a genuine large area capability of up to 50 x 50cm. It used a unique optical design which enabled use in a normally lit environment. In essence it was the first “useable” laser Doppler imager albeit in a working prototype form (that worked exceptionally well!). Tim and Philip had partnered with the British Technology Group to seek a commercial partner. The BTG have a long history of aiding commercialisation of inventive academic research having triumphed in (to name a couple) commercialisation of MRI and patent defence of the hovercraft - successfully defending the UK patent against The Pentagon in Congress. BTG currently hold a very diverse array of ~8000 patents…



Having commercial and technical experience and customer feedback of the Swedish system, we decided to break ties there and move forward with further developing and commercialising the vastly superior Newcastle system signing an agreement in 1995 with BTG. It is worth noting that this system (albeit in a grandchild form) is still available from us today and forms a key part of our imaging portfolio. The system uses a single laser beam (like a laser pointer) moving across the tissue continuously rather than in a stepped fashion making the scanning much more rapid without compromising accuracy.

Early Evidence and Market Research

As part of the due diligence process, we were given access to a number of test images taken at Newcastle hospital together with scientific publications. One of the publications applied the LDI technique to burn assessment and whilst the study was small (10 patients) it was a significant indication for us of how the technique could be developed into a clinically useful tool. This publication proved to be “the acorn moment”.



Further research showed that at this time, how you were treated as a burn victim largely relied on the clinical experience and eyes of the surgeon. However, even the best surgeons were honest that, at times, in the more difficult cases, accurate diagnosis was incredibly difficult. In those cases, the standard procedure would be to wait and see how the burn healed (or not) to decide whether a burn should be grafted or not waiting maybe, upwards of two weeks. It seemed somehow as if burn victims had been left behind in hospital diagnostics at a time when it would be unthinkable not to have an X-ray for a broken bone, or an ultrasound scan if pregnant. Thus, we resolved to produce a system that would aid the burn surgeon with more accurate diagnosis and as early as possible after the burn to minimise time to surgery if needed. Thus the Newcastle publication, and this prototype, came together at the right time for us to embark on what would become a major investment project to help revolutionise patient care aiming to make burn assessment much less subjective and more consistent.

Development and Commercial Realisation

Whilst the Newcastle prototype was working (and could scan a patient across a room!), it was large and wall mounted. Our designers focussed on making the system smaller and more mobile, without compromising performance. To put the time scale in context, we eventually launched the first system with brand new control and analysis software on the new Windows 3.1 platform at a time when the Swedish system was still using the MS DOS environment.

Early Adoption

Without ignoring other research applications (spoiler alert - more in Article 3!) we started to attend Burn Congresses routinely – The British Burn Association, European Burn Association, American Burn Association and the Australia and New Zealand Burn Association for example. Interest in the system was keen as it was recognised by Burn Surgeons that there was nothing else other than experience to aid diagnosis in the more difficult cases. Critically important relationships formed at this stage with leaders in the field endure today and include groups such as Newcastle, Gent, Washington, Sydney amongst others too numerous to mention (but essentially a Who's Who of burn specialists).

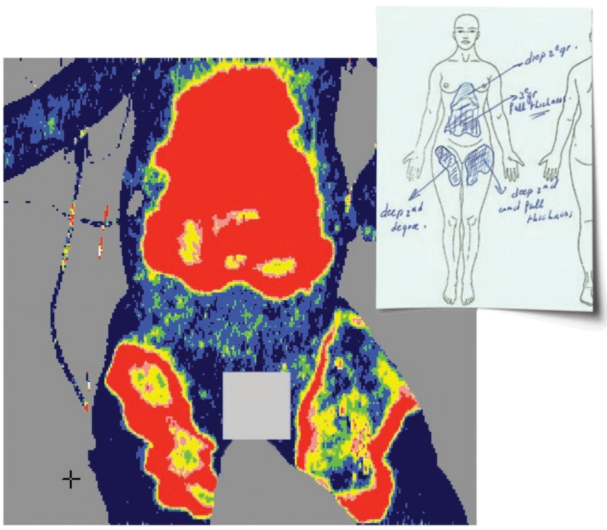
Early adopters used our standard research software and hardware but we quickly realised this couldn't be the final solution that would gain widespread use as we received more feedback.

In order to offer a system that could be used easily and safely in theatre and bedside, we refined the moorLDI into moorLDI2 which featured a sealed "through window" design for ultimate patient safety and a digital camera for colour photograph of the burn. This enabled us to compete for, and win a DTI Government SMART award in 2001 to develop the technique and embark on a multi centre clinical trial to further refine the software and hardware.

Burn Classification and the Concept of Healing Potential

At this time, the traditional burn depth classification system (1st, 2nd, 3rd degree) was challenged as the leading centres we were working with were also using innovative treatments that could alter whether a burn that would have been treated with surgery could be treated without. “Predicted Healing Time” became the diagnosis of choice and working with imminent statisticians, we developed a unique colour palette that gave just that. Scan the burn and get a colour coded map, the colours of which predict how long the burn will take to heal allowing the surgeon to choose the treatment plan based on what was available to the consultant. Importantly, it was shown that the diagnostic accuracy could be improved from 50% - 70% to >95% (together with the clinicians opinion) from just two days post burn, a time when visual indications of burn outcome are notoriously difficult otherwise.

Together with hardware changes, the new software really was the heart of our new MK II clinical tool.



“Diagnostic image of young infant with three burn areas most of which was predicted to heal without surgery by LDI, contrary to clinical opinion”

Adoption of the new MK II system started most notably in the UK and in Australia (with the help of our long term distributor, SDR Technology, based in Sydney), where today (along with the UK) the vast majority of Burn units are equipped with our systems. It should not be underestimated the importance our key opinion leaders had in presenting their findings using the new system on a global platform, spreading the word and helping uptake.

Clinical Trial #1, FDA and NICE

It became apparent that although we were convinced of the benefits, only clinical trials would prove the clinical pedigree we needed. Around 2007, the evaluation of our first five year multi-centre clinical trial came to fruition with our own in-house clinical specialists working alongside key centres in Newcastle, Gent, Baltimore and Washington. Help with the statistical analysis came from UK researcher Rose Baker and the technical skill of in-house software and hardware designers helped bring together a step change in patient diagnosis the system becoming the first ever (and still the only), CE registered (European) and FDA 510k registered (USA) diagnostic system for clinical burn assessment – an important milestone!

Simultaneously, we wanted to seek independent verification that implementation of our technique was both clinically and cost beneficial so we worked with the National Institute of Health and Care Excellence, a UK Government body whose remit is to evaluate claims made by equipment and drug suppliers and make informed recommendations to the NHS, our UK Government health system. After evaluation, we received the verdict that it did make financial sense to implement the technology alongside the patient benefits on offer.

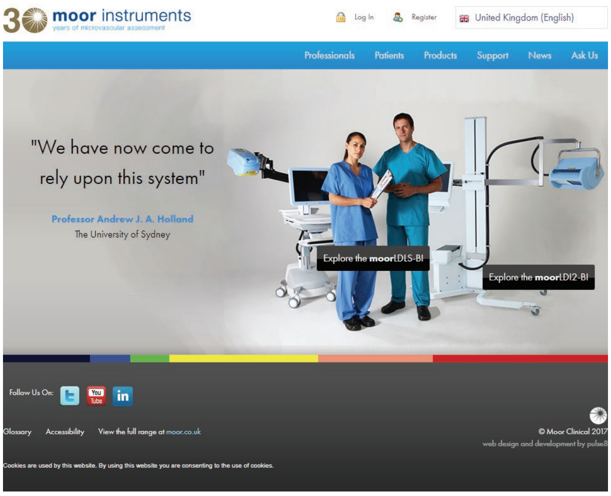
moorLDLS Line Scanner, Clinical Trial #2 and Medilink Award

Back at Moor though, software and hardware development continued ceaselessly and we patented a new imaging system which would become the moorLDLS-BI. We had recognised that not all burns were large and that not all patients could stay still for long enough to obtain a clear scan (children and the elderly). Thus the new system was intended to target that issue. Rather than using a single beam, the new system used a line projected onto the tissue to sweep quickly across, taking just four seconds to generate an image. A second multi-centre clinical trial in Gent, Sydney, Birmingham, and Dayton was completed in 2013 to establish clinical equivalence between the moorLDI2-BI and the moorLDLS-BI and subsequently the NICE recommendation was modified to include the new imager. The software had evolved considerably and we now offered our unique colour palette in all versions of burn software, a patient database, DICOM compatibility and a multi-lingual, user friendly design.

In 2014 we were proud to be awarded the Medilink “outstanding achievement” award recognising that “Over the past decade, they (Moor Instruments) have advanced laser Doppler imaging technology from a purely research tool in to a dedicated medical device for burn assessments in clinical settings”.

Today and The Future

Today, we offer both systems, the moorLDI2-BI, large area imaging typically for adults and the moorLDLS, rapid imaging for paediatric centres. We supply both directly and through a network of distributors globally (including sister companies in the US and Germany). We have cemented our position as the ONLY global providers of diagnostic burn imagers that have clinical and scientific pedigree, backed by appropriate certification in major markets for clinical diagnosis. We also launched a website dedicated to clinicians and patients alike (www.moorclinical.com)



Uptake of the unit has been solid and our global reach is spreading. Our aim is that every burn victim will ultimately have access to the diagnosis and it has been a source of great pride that we have been able to step in and assist at critical times – our systems helped victims of the Bali bombings for example and more recently the Bucharest nightclub fire. We support and are in admiration of a number of centres and charities, including a close association with Dans Fund for Burns whom we are happy to provide a platform for at the British Burn Association each year.

Burn Assessment imaging has been a defining project for us and we will continue to devote our time to further improvements but, it is by no means our whole imaging story. Our next article will focus on other applications and imagers and how their availability is contributing to research into stroke, wound healing, tumour suppression and stem cell therapies.

As always, if you have any questions about this article, please feel free to contact us!

References

"A new medical instrument is presented that produces a doppler blood flow image from a laser beam in a raster pattern and the results of a pilot study which shows this technique to be highly accurate in assessing burn depth is described."

Niazi, Z.B.M. Essex, T.J.H. Papini, R. Scott, D. McLean, N.R. Black, M.J.M. (1993) New laser doppler scanner, a valuable adjunct in burn depth assessment **Burns.** Volume 19, Issue 6, December 1993, Pages 485-489.

"We have devised a new colour palette for LDI burn imaging based on healing times of a series of burns."

Pape, S.A. Baker, R. D. Wilson, D. Hoeksema, H. Jeng, J.C. Spence, R.J. Monstrey, S (2011) Burn wound healing time assessed by laser Doppler imaging (LDI). Part 1: Derivation of a dedicated colour code for image interpretation **Burns.** 38 (2) p187-194.

"LDI can be used in a standardised way as a valid tool for improving on clinical assessment of burn wounds. This can enable earlier appropriate management."

Monstrey, S M. Hoeksema, H. Baker, R D. Jeng, J. Spence, R J. Wilson, D. Pape, S A. (2011) Burn wound healing time assessed by laser Doppler imaging. Part 2: Validation of a dedicated colour code for image interpretation. **Burns.** 37 (2) p249-256.

"The high accuracy of the new line-scan imager was comparable to that of the traditional LDI. Its size and mobility enabled easier ward and outpatient use. The higher scan speed was particularly beneficial for scans in paediatric patients."

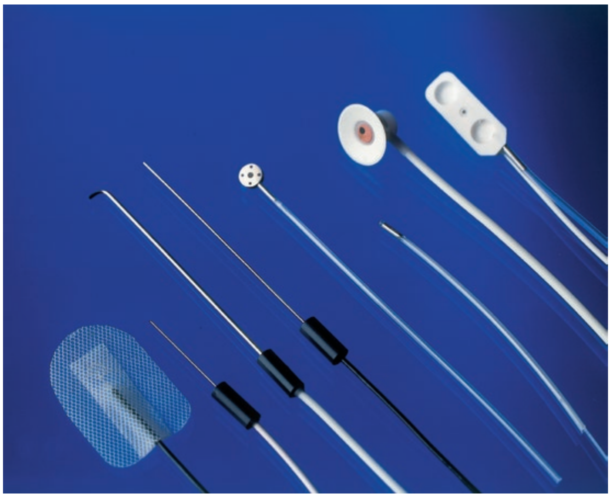
Hoeksema H., Baker R.D., Holland A.J.A., Perry T., Jeffery S.L.A., Verbelen J.F., Monstrey S. 2014. A new, fast LDI for assessment of burns: A multi-centre clinical evaluation. **Burns**, Vol 40, pp 1274-1282.

Blood flow imaging – Missing links, Robot Wars and how to get colour images from a black and white camera…

We hope you have enjoyed the first two articles to help gain an insight into Moor Instruments and to help celebrate our 30th year in business. Article 1 focussed on our founding and range of laser Doppler monitors and Article 2 focussed on how we developed the Burn Assessment system and market (www.moorclinical.com). In this, Article 3 (of 4) we focus on the expansion of our product range from monitoring into imaging.

Laser Doppler Monitoring

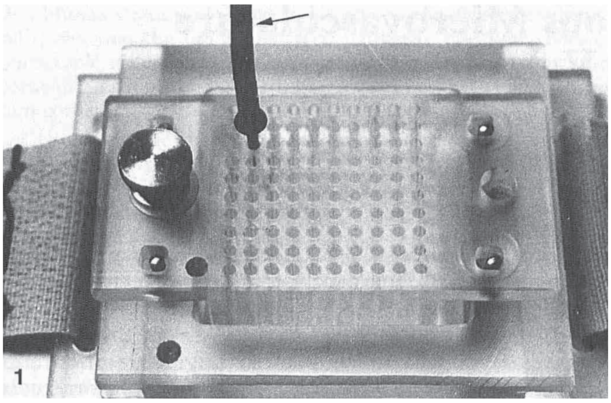
Whilst the laser Doppler monitor was our founding product and still offers unique advantages that make it relevant today, the technique always requires a probe in contact with tissue to generate a measurement of blood flow in a very discrete sample volume. The strength of the monitoring technique is in looking at changes in blood flow over time, usually due to a provocation (e.g. pressure cuff, vasoactive drug delivery, tissue heating etc). With a range of probes for skin, endoscopic use, muscle, teeth etc the monitor has always been versatile and able to access tissues that could not otherwise be examined easily.



However there was always an interest in spatial variations in flow – or a blood flow “map” - and without the potential influence of probe contact and the sterility issues that creates. Thus the need to develop laser Doppler Imaging...

The Missing Link…

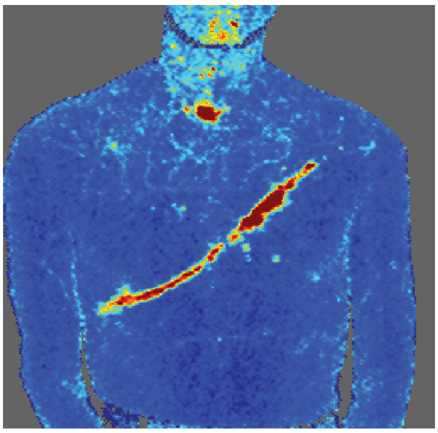
Experimentally, one crossover technique was an adaptation of monitoring by Professor Irwin Braverman in Yale, who used a perspex square with holes drilled in a grid to allow mapped placement of a laser Doppler probe reproducibly over an area, subsequently producing processed grey scale images to show areas of high and low flow. This technique still relied on tissue contact though which is less optimal for patient measurements, particularly for those who are suffering from painful wounds. But: Prof Braverman was amongst the first (if not the first) to generate blood flow images and could clearly identify ascending arterioles for example. Simple, but very clever. Monitoring? Yes. Imaging? Yes Also! We would later have the pleasure of meeting Prof Braverman and showing him our imager, moorLDI, on its first US promotional tour.



Around this time, a system was produced and commercialised in Sweden by Lisca Development that used a laser beam, directed onto the tissue by two moving mirrors and stepped motors to move the beam in a raster pattern across the tissue – emulating Bravermans model and thus becoming the first mechanical laser Doppler imager. For a short time Moor became the UK distributor of the system although the early feedback was that the system was very slow in use, required semi-darkness and only offered 64 x 64 pixels covering a small, hand sized area in ~5 minutes. It became obvious this unit would not gain clinical acceptance so we started work on our own, based on a patented technology transfer prototype from Newcastle (refer to article 2 for more information).

moorLDI

We subsequently launched the moorLDI which offered flexibility up to 256 x 256 pixels – 16 x the number of pixels of the Swedish. The moorLDI could map an area up to 50 x 50cm with clinically useful resolution in a relatively modest 2 minutes. The faster, larger, high resolution scan was made possible with a patented continuously moving beam and a large single mirror design that was used both to direct the beam onto the tissue and also to collect reflected light from the tissue which was focussed onto photo detectors with a lens system. The improved optical design enabled the system to be used in normal room lighting, finally enabling practical use in a hospital environment, on human subjects. The system was made easy to use with the use of Windows based software designed to run on the Microsoft 3.1 platform bypassing DOS (for those of us who remember what that is!) altogether. For the first time we could start to think of clinical applications for the imaging technology (refer to article 2 to learn about Burn Assessment).



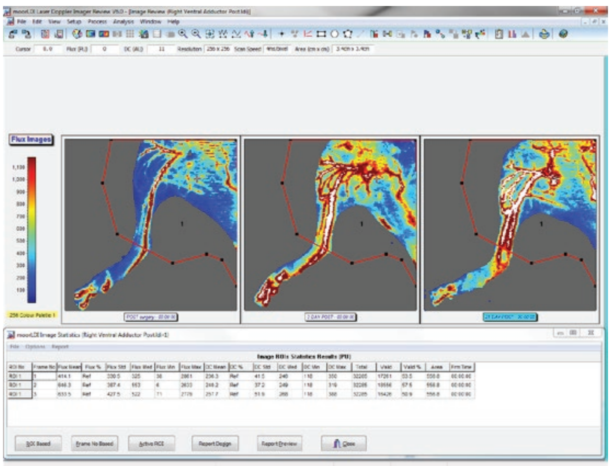
moorLDI2

The moorLDI became a key financial success for us and enabled continued expansion and with profits ploughed back into the business, we could soon consider the replacement for moorLDI. Aesthetically the system left a little to be desired so we engaged external consultants to design a new, moulded case with built in handles to ease positioning. We also found customers in the clinical setting were interested in colour photographs of what they were imaging – so we incorporated a colour CCD camera which not only provided the additional documented information but also allowed us to offer automatic distance measurement so we could correct measured flow values to a common calibrated scale (perfusion units) regardless of whether small (close up measurement) or large area (distant measurements). Infection control also became an issue, so the open window design was replaced with a suitable glass window which would allow the system to be “fogged” in the theatre environment.

Variations…

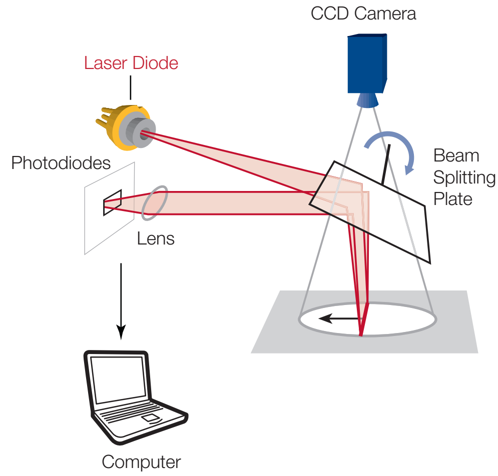
A handful of customers had quite exacting needs and unique requirements and over the years we produced a number of variants, using different wavelengths to access different tissue beds, even incorporating two lasers in one system to scan from different beds at the same time (moorLDI2-SIM). Although functionally it was one of the most advanced options, looking back now, aesthetically it wouldn't have looked out of place on robot wars.

One variant that really gained momentum was the moorLDI2-HIR (High resolution). This was specifically designed for the hind limb ischemia model and featured a longer, 830nm wavelength and focussed optical design for superior penetration to allow visualisation of collateral vessel formation. We also include fine pitch encoders to limit the scan area from 2.5 x 2.5cm to 5 x 5cm (although larger areas are possible). This variant remains popular to this day offering 100 micron resolution.



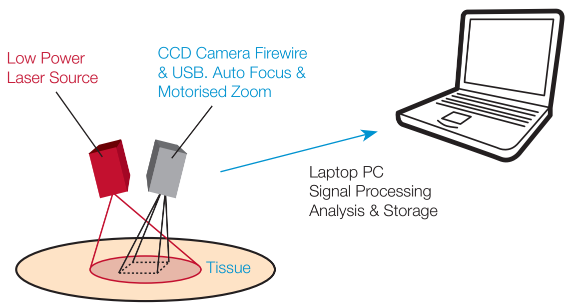
Line scanning with moorLDLS

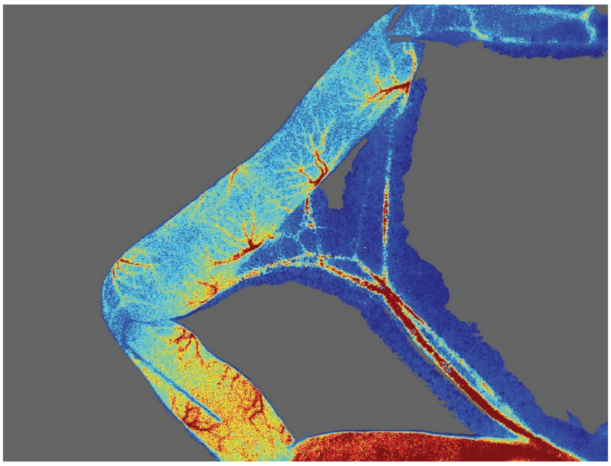
There was still a clinical need for faster scanning, despite moorLDI2 being relatively fast so our engineers embarked on a novel patented solution. Instead of a single beam scanning back and forth, building up the image pixel by pixel, line by line, we decided to project a laser line onto the tissue and capture the entire image in one sweep, with a series of photodetectors. This made total image acquisition possible in just 6 seconds as the line swept across the tissue making it ideal for burn assessment of paediatrics and the elderly, two groups who we learned found it hard to pose stationary for a regular image. The scan head was smaller and we could offer a smaller mobile stand, with self contained PC and battery backup.



Laser Speckle – moorFLPI

Laser Doppler monitoring and imaging had served us very well, but looking at what could be the next imaging step, laser speckle contrast (AKA LASCA and Full field perfusion imaging) became an obvious choice to develop. This technique illuminates an area with low power laser light and uses a black and white CCD camera to pick up changes in the random speckle pattern that is generated. The changes in contrast can be processed in various ways to generate flow images very quickly, with very high resolution. The first prototype took just 6 weeks to develop (although the production version, moorFLPI would take much longer!). Very quickly the potential became obvious. For the first time we could see "blood flow videos" enabling the study of variations in flow, both spatially and temporally. Using a zoom lens meant we could study large and small areas with one system. Laser Doppler had become so well published and established that it took a little while for customers to adopt the new technique, but both moorLDI and moorFLPI still offer unique advantages that make them both relevant today.

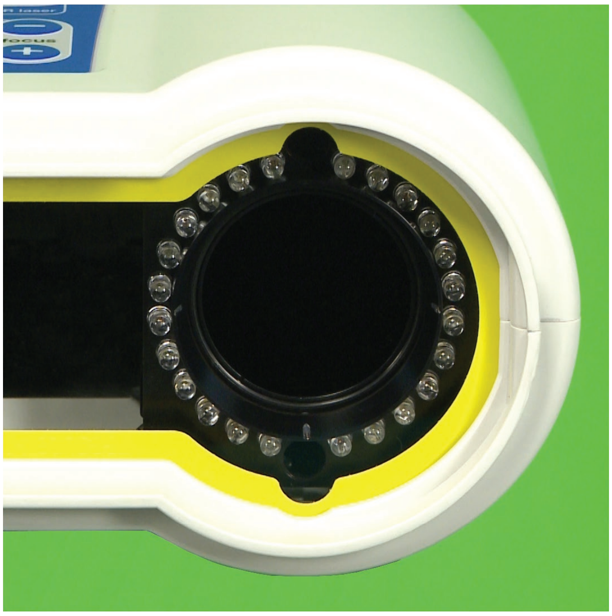




To the present…

We still sell moorLDI2 today, although we have refined the electronics considerably. With a new clinical mobile stand this unit forms the basis of our burn assessment system. The HR variant we developed has become one of the mainstream offerings for hind limb ischemia, where larger animals or a deeper penetration is needed. The Swedish laser Doppler never caught up and is discontinued so we have become sole providers of laser Doppler imaging globally. The moorLDLS has also been refined again, with a more compact electronic design. This has become stablemate to the moorLDI2-BI enabling us to offer a dedicated burn assessment solution for adults and children alike. We also offer moorLFPI2 – a much improved version of moorFLPI. This unit offers a motorized zoom and auto focus for small and large area imaging from one model. With a unique RGB area illumination of the scan area, we can produce a composite colour photo from the same black and white CCD camera that is used for measurement – clever stuff indeed!

Over the years we have established ourselves as global experts in blood flow imaging, and with a core offering of 5 imagers we will have an optimal solution and the widest application experience for you.



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Applications - Routine, Weird and Wonderful!

As celebrations conclude on our 30th year in business, the final article in our series of four to help document our history focusses on the applications that have been enhanced with the use of our technology, both imaging and monitoring.

For those who are fresh to our products, we typically explain that our products are used to assess changes in blood perfusion in the microcirculation, either over time, or spatially, or both. This is easily demonstrated with a scratch to the back of the hand, a Valsalva manoeuvre, raising the hand, use of a pressure cuff etc. In the resting state, the techniques are sensitive enough to pick up variations due to the beating heart, breathing, vasomotion along with other slow wave oscillations.

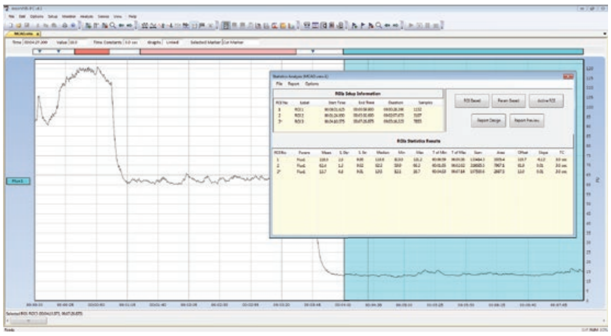
The techniques bear similarity to ultrasound and share the use of the Doppler principle, although we use lasers instead of sound to focus instead on the much smaller peripheral vessels. The measurement volume is from the tissue surface down to an estimated 1-2mm. The precise sample volume is unknown - it varies according to the tissue sampled and the technique used. For that reason, it is not possible to define an empirical perfusion unit (such as ml/100gm/minute for example). Instead, laser Doppler/ speckle offers a range of perfusion units, normally 0-1000 for monitors or 0-5000 for imaging. Part of the validation process includes using a flow model to ensure linearity in the instrument response. Most often the results are interpreted as a percentage change in baseline flow or from surrounding tissue, usually due to a standard stimulation.

Skin probes were the first to be developed but the range has developed to enable easier and more convenient measurements in a wide range of situations. This opened up the range of applications enormously and has led to some core applications in both animal and human studies

1. Stroke modelling / MCAO

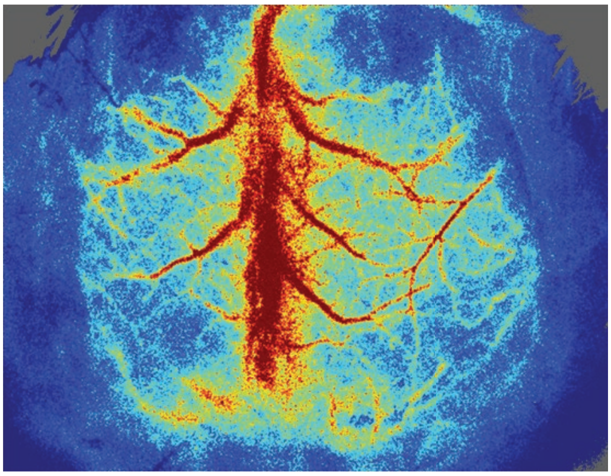
A technique for experimental stroke modelling was described first by Tamura et al of the Wellcome Surgical Institute in Glasgow, Scotland as far back as 1981. The model was described in the first journal of the ISCBFM. Although laser Doppler wasn't used to confirm the reduction in flow caused by the artery occlusion (mainly because there wasn't a commercially available system back then), it does represent an important milestone moment.

The key advantage of applying laser Doppler to the model was in following the blood flow changes through the skull in real time and at the time of surgery to quickly confirm the flow reduction (typically to 10% of baseline). It was also more accurate at predicting the stroke condition enhancing and optimising research outcomes. It is hard to identify who first published use of laser Doppler as a means to confirm experimental stroke, but we think it was Barone et al using a commercial LDF from the US, presented at the First International Conference on Stroke, Geneva, Switzerland, May 30–June 1 in 1991.



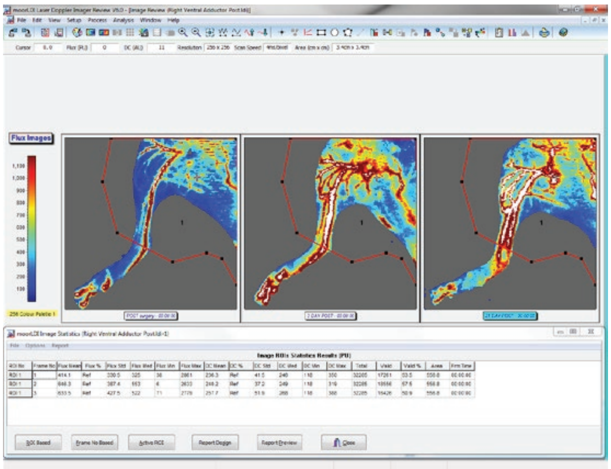
The technique was first used in Europe by Reulen et al based in Germany who first used our MBF3D monitor. The trace above shows the typical flow reduction profile (sample data reproduced with kind permission from Dr C. Gibson, Leicester University, Leicester, UK).

Today, this has grown to become one of the more common applications and at SfN last year (the largest Neuroscience gathering in the world) there were over 430 posters on MCAO from 28 different countries. Laser Doppler monitoring has now become the gold standard to enable researchers to allow their models to progress to other therapeutic drug treatments, usually with the end aim of developing drugs that can help human patients in a stroke situation. There is already keen uptake of laser Speckle imaging to study spatial and temporal changes, useful tool for studying cortical spreading de-polarization without contact.



2. Hind Limb ischemia/ Angiogenesis modelling/ HLI

Laser Doppler Imaging is a well-established technique used to assess global blood perfusion in the hind limb of mice and rats non-invasively and without the use of tracer dyes. This enables the comparison of blood flow in a limb where flow has been reduced by ligation, relative to the control limb. The measurement can be performed over a number of days so that reperfusion enabled by the development of collateral vessels can be assessed. Femoral artery ligation will result in much reduced flow in the limb (typically 80-90% one day post).



Therapies designed to enhance the angiogenesis process can be identified by a more rapid return to baseline blood flow levels (100%) i.e. the same flow as control limb. Such therapies would find application in speeding up wound healing processes.

Therapies that are designed to inhibit angiogenesis can be identified by a slower return to baseline compared to normal. Such therapies are useful to suppress flow – and can be useful to study restriction of tumour growth.

Application of LDI: Originally the model relied on injecting tracer dyes and use of an animal at each time point to check relative flow between the ligated and non-ligated limb. Application of laser Doppler meant that the analysis could be performed in vivo and non-invasively and the same animal could be used for numerous time points, greatly reducing the number of animals needed for study and enhancing the accuracy and reproducibility of data. Dr Jeffrey Isner and his team are widely credited as the pioneers of this type of work at St Elizabeth's Medical Center, Tufts University, USA. This early work was quickly adopted globally, particularly in Japan, where interest in the re-invented model boosted sales considerably. At the recent American Heart Association conference, there were around 30 HLI posters, the majority using our imaging systems. We currently provide two imaging systems for HLI. The laser speckle technique (moorFLPI2) offers the highest spatial resolution and can be used to assess reperfusion in the pads of the feet, an alternative technique that avoids the need for limb hair removal. We also offer the unique, high resolution laser Doppler imager (moorLDI2-HIR) with a fine pixel resolution of 100 microns and a superior penetration that is ideal for studying collateral vessel formation

3. Vascular Assessments of the microcirculation. Toe Pressure.

We have already highlighted that our monitors and imagers detect flow in small peripheral vessels found in the microcirculation and can record increases and decreases in blood perfusion as these vessels dilate and constrict. Often disease can affect these processes though and focussing on the function of micro-vessels at the extremities has been used as an early predictor those studying diabetes, hypertension, Raynauds etc. for some time. Changes in function are typically assessed by measuring responses to standard flow challenges, such as pressure cuff occlusion, tissue heating and vasoactive drug delivery.

Early interest in micro-vessels dates back to the late 1920's where Kernohan, Anderson and Keith published "The arterioles in Hypertension". However, functional measurements came a little later and a number of references followed on from Kernohan, Anderson and Keiths publication. One reference where specific interest in toe pressure is noted is from 1971 when Carter and Lezack used "the appearance of a pink "flush" in the skin of the digit, previously blanched" to determine the blood flow return. This is possibly the pre-cursor to today's functional toe pressure measurements.

Toe pressure measurements involve placing a cuff around the large toe and occluding flow by increasing the pressure in the cuff. Once flow has ceased, the pressure in the cuff is decreased slowly to the point where flow returns. The pressure in the cuff at the point where flow returns is defined as the "systolic toe blood pressure"

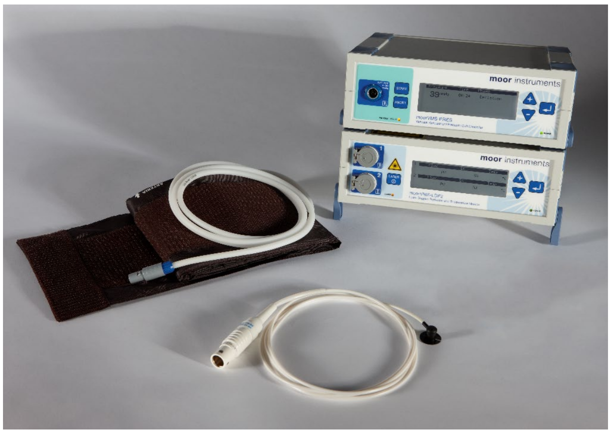
How to assess flow return though? Changes in colour was used by Carter and Lezack back in 1971. They also used mercury in rubber strain gauge plethysmography to detect changes in toe volume caused by return of blood to the toe. The "whooshing sound" of blood returning is used for conventional blood pressure measurements, but doesn't easily apply to the toe partly because calcification in the vessels of toes affected by PAD means flow return is often impaired also negatively impacting the effectiveness of more sophisticated techniques such as ultrasound or "pocket Doppler" are not always useful.

This is where the strength of laser Doppler comes in as minute flow changes in the diseased vessels can be detected. Comparisons of laser Doppler vs photo plethysmography began in the 1980's as commercial systems became available.

The potential to automate these standard processes was first exploited by Moor in collaboration with E. Wahlberg et al of the Karolinska University Hospital where a prototype laser Doppler/ Pressure cuff controller was used. This forms the basis of what we offer today with the VMS modules and VASC software to ensure reproducibility and ease of use over manual control.

For pressure cuff stimulations, we have replaced manual, hand inflation, a stopwatch and an analogue pressure dial with Protocol Control - hands off, automated, digital control. The automation and ease of use now extends to analysis of either individual measurements or batches of measurements.

Such measurements extend now to a full range of vascular assessments – skin perfusion pressure, post occlusive reactive hyperaemia, pulse volume etc.



Typically found in the leading vascular clinics, we anticipate that these measurements will become more routine in a clinical setting.

We hope you have found these four articles informative and interesting. In this article we have covered three typical applications of our blood flow monitoring and imaging systems. Our systems have been used in numerous other clinical research and pre-clinical applications. More information can be found on our website, www.moor.co.uk. If you have a specific interest, as always, we encourage any questions or suggestions and would welcome the chance to discuss how we might help with your own research applications and plans.

To all our customers over the years – we thank you and look forward to continual fruitful collaboration and support!