PATHOLOGY IN PRACTICE

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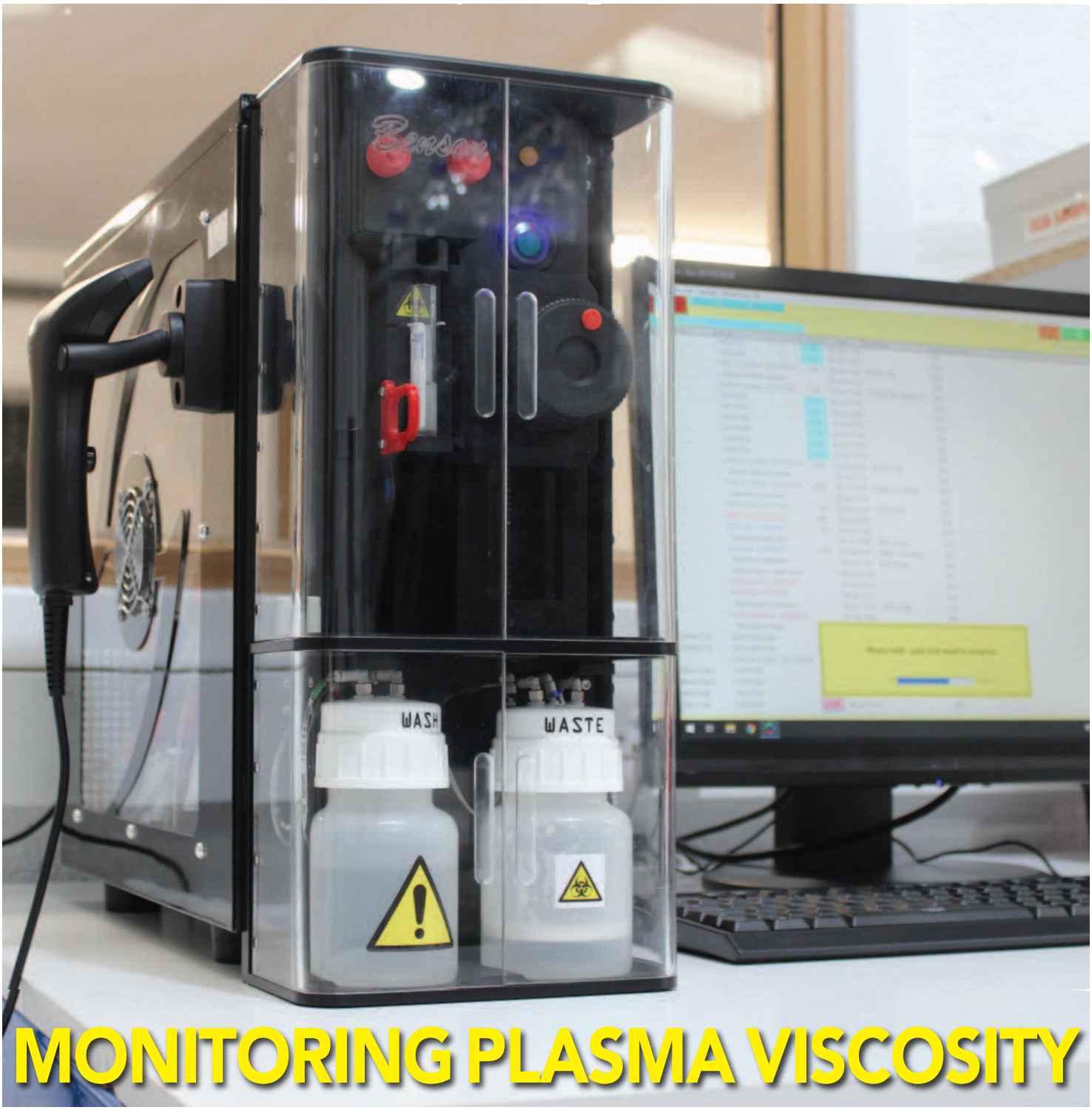
THE PV TEST IS STABLE, TECHNICALLY REPRODUCIBLE AND STANDARDISED

THE PV TEST CAN BE PERFORMED ON A SAMPLE UP TO SEVEN DAYS OLD

MANY CLINICIANS RECOMMEND THE PV TEST FOR ITS SENSITIVITY



MONITORING PLASMA VISCOSITY

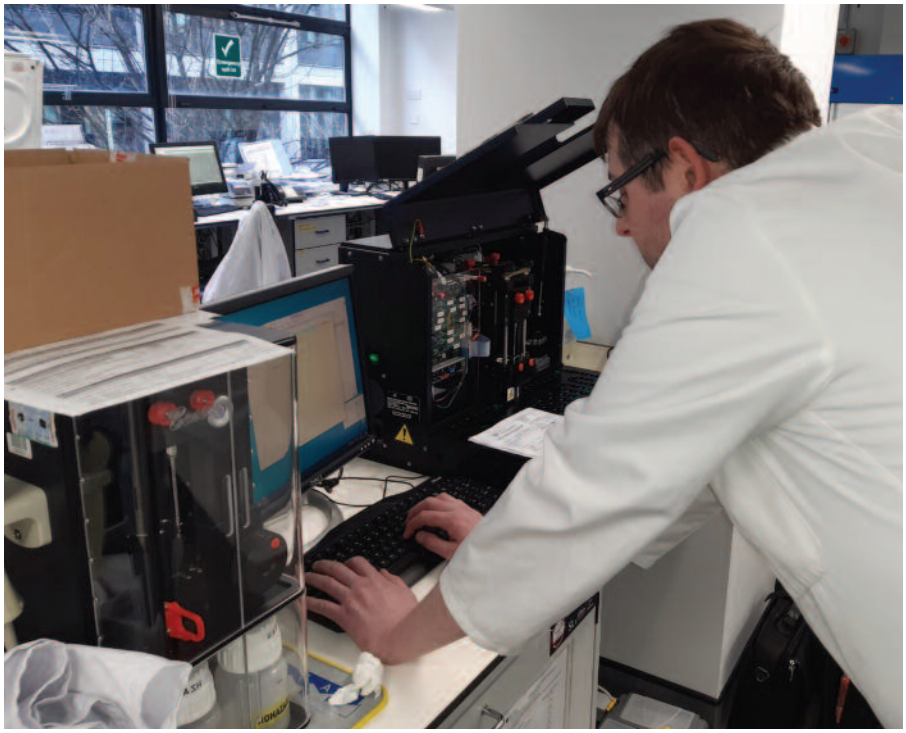
Plasma viscosity in COVID-19 disease: a vital monitoring role

Establishing the diagnostic and prognostic value of measuring plasma viscosity in patients suspected or confirmed as having COVID-19 is currently underway in several UK hospitals. The following article provides an overview of progress in research and practice.

The coronavirus SARS-COV-2, which emerged in late 2019, continues to spread around the world, having infected more than 4.5 million people at time of writing, and leading to more than 300,000 deaths. The COVID-19 disease presents a rapid learning challenge for everyone involved in battling with the condition.

While widely regarded as primarily a respiratory disease, it is increasingly being recognised by doctors and scientists as a systemic infection, which affects not only the respiratory tract, but also the central nervous system, musculoskeletal, renal, haematological and hepatic systems.

The haematological clinical manifestations of COVID-19 are receiving increasing attention, as the scientific and medical community work hard at trying to solve some of the many questions posed. For example, why is it that some patients have severe symptoms while others have relatively mild symptoms? What is the pathology of the emerging phenomenon of the Kawasaki-like illness linked to COVID-19, which has coronary artery aneurysms as its main complication?[1] Why do a substantial proportion of severe COVID-19 patients develop venous and arterial thromboembolic conditions, and what can we do to improve early recognition of these?[2] Haematological investigations are going to be critical to solving these and other emerging questions. Many of the supporting answers could lie in plasma viscosity.



Plasma viscosity at University College Hospital in London using BV1 and BV200.

Plasma viscosity testing

Plasma viscosity testing is a sensitive index of plasma protein changes that result from inflammation or tissue damage. The plasma viscosity (PV) test is well-established in many NHS hospitals, including some at the forefront of the fight against COVID-19, such as University College Hospital and St Thomas' Hospital in London, and Addenbrooke's Hospital in Cambridge.

It is a highly accurate indicator of many conditions including any inflammatory

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While initially a respiratory disease, COVID-19 is increasingly recognised as a systemic infection.

The Benson BV1 viscometer.

disorder (eg infection, rheumatoid arthritis), tuberculosis and polymyalgia rheumatica/temporal arteritis. It is also used as a marker for subsequent adverse events in angina, stroke and peripheral occlusive vascular disease. Plasma viscosity is used as a screening test but, unlike some other indicators and inflammatory markers, it is not affected by haematocrit variations (eg anaemia or polycythaemia) or gender, patient age, exercise, pregnancy and age of sample.

Many clinicians recommend the PV test for its sensitivity. Other benefits of the test are that PV becomes abnormal early in the disease, has a low incidence of false-normal values, can be performed on a sample up to seven days old, is stable, technically reproducible and standardised, and that relatively small changes are significant for any individual.

As with any infection, SARS-CoV-2 will cause an increase in the release of acute-phase proteins into the circulation. Plasma viscosity could be a particularly useful way of measuring this as it is known to show a significant increase in a range of different types of infection, including viral and bacterial.

Early identification of severely-affected patients

Benson Viscometers, a global leader in the clinical measurement of plasma viscosity, is currently exploring the possibility with partner laboratories of early identification of COVID-19 patients who subsequently go on to develop severe symptoms. This is important because early intervention could increase the likelihood of early recovery. Daniel Gleghorn, a senior biomedical scientist at Cambridge University Hospitals NHS Foundation Trust, says: "We are interested in establishing the diagnostic and hopefully prognostic value of measuring the plasma viscosity of patients suspected or confirmed as having COVID-19. We are looking at determining a cut-off level for those patients who are positive and additionally following several patients' progress through the condition, regularly monitoring their PV level."

A symptomatic or confirmed person with COVID-19 will probably have an increased PV above the normal range. The patient's result is likely to continue rising if their condition deteriorates, until their immune response successfully has the infection under control. A rising daily PV may indicate that a COVID-19 patient is developing severe symptoms and requires more intensive therapy, such as oxygen support in the form of CPAP or IPPV (ventilation). Similarly, a fall or plateau in PV could be indicative that a patient is over the worst of the infection and that they therefore require a less-intrusive approach.

Identification of recovered patients

While the patient is in recovery, the PV result is likely to begin to fall. However, paradoxically, most patients are likely still to have a positive antigen test. It is proposed that the start of the reduction in viscosity, when measured on consecutive days, could be used as an indicative marker of patient recovery. Hence the patient and their relatives could be informed potentially earlier than at present that there is an indication of recovery, thus reducing anxiety for clinicians and families. If a daily PV monitoring routine is started as early as practical, a record of the disease's progress will be available to aid clinicians in determining the most appropriate treatment. With data analysis and experience, they will then be able to forecast and prepare for a worsening condition if the data show a patient's condition is deteriorating.

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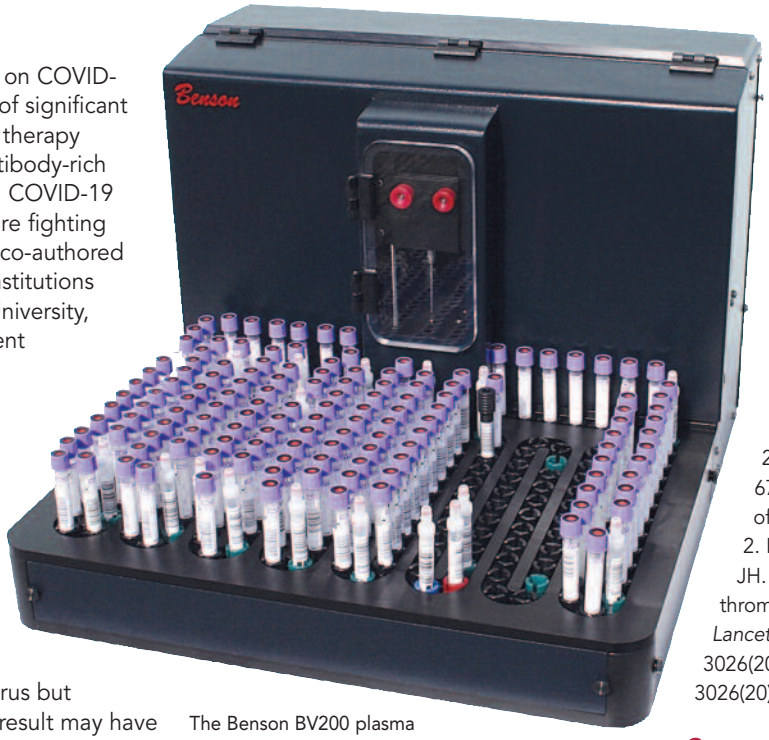
Plasma therapy

The use of plasma therapy on COVID-19 patients is also an area of significant interest. This experimental therapy involves transfusing the antibody-rich blood plasma of recovered COVID-19 patients into people who are fighting the illness. A recent study, co-authored by researchers at several institutions including Michigan State University, has shown that the treatment is safe. Plasma viscosity measurement could be an important next step in establishing its effectiveness.

As one of the parameters that raises the PV result is the concentration of antibodies in a person's plasma, patients who have recovered from the virus but maintain a raised viscosity result may have a high-titre antibody level, which would suggest they could be suitable donors for plasmapheresis to provide antibody therapy protection to other patients.



The Benson BV200 plasma viscosity analyser (clinical viscometer).

Research

The hypotheses involving PV are based on anecdotal evidence and need to be proven through clinical laboratory trials. Bernie Benson, founder of Benson Viscometers, says: "We are seeking to work with clinical and academic groups, potentially to form partnerships to undertake the required analysis. If anyone is planning to undertake a study or trial, we would welcome discussions to progress this. The plasma viscosity test could be specifically used as part of local COVID-19 screening blood work and also to monitor the intensity and progress of the virus episode in a patient, especially given most hospitalised COVID-19 patients are already having daily haematology and chemistry profiles carried out."

Safe, inexpensive and precise

For safety reasons, laboratories are applying the principles of 'closed vial sampling' more rigidly now and, as a result, any test on a COVID-19 patient that is underfilled or requires the sample top to be removed is generally refused unless in exceptional circumstances. The PV analysis is carried out without removing the sample tube cap so is ideally suited to the current circumstances and will provide rapid and straightforward numerical results. There is one normal range for all ages and both sexes (1.5–1.72 milliPascal-second [mPa•s]), which is already well established and documented for over 50 years, meaning results interpretation is straightforward and there is no requirement to establish a normal range.

Plasma viscosity is a safe and inexpensive test that is capable of a precise result with a high level of confidence within minutes of a blood sample arriving in the hospital laboratory. All the NHS clinical viscometers in use are manufactured and supplied by a British company. They are already operational, programmed and linked via the NHS laboratory information management system (LIMS), enabling hospitals to manage samples effectively and automatically communicate results and associated data. Therefore, obtaining results for a multi-centre trial is easy.

Conclusions

The role of plasma viscosity in COVID-19 is an avenue which cannot be ignored. In the battle against the disease, we need the shared knowledge and contributions of research, statistical analysis and 'lessons learned' from a wide range of disciplines.

Haematology is emerging as a discipline with a crucial role to play. The PV test will play a significant part in that, as both an individual test and as part of a routine blood work-up panel. To facilitate this, there now needs to be as many PV tests performed as possible to provide large amounts of meaningful data that can be evaluated and statistically analysed to assist with COVID-19 and also with any future pandemics.

For any laboratories with a reduced routine workload volume, this is an opportune time to utilise available capacity and existing equipment to support finding the answers to COVID-19.

References

1. Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. *Lancet* 2020 May 13. doi: 10.1016/S0140-6736(20)31129-6. Online ahead of print.

2. Levi M, Thachil A, Toshiaki I, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 2020 May 11: S2352-3026(20)30145-9. doi: 10.1016/S2352-3026(20)30145-9. Online ahead of print.

Suggested further reading

- Cao M, Zhang D, Wang Y *et al*. Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai, China. medRxiv preprint doi: 10.1101/2020.03.04.20030395.
- Fan BE, Chong VCL, Chan SSW *et al*. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol* 2020; **95** (6): E131–E134. doi: 10.1002/ajh.25774. Epub 2020 Mar 19.
- Klok FA, Kruip MJHA, van der Meer NJM *et al*. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020 Apr 10: S0049-3848(20)30120-1. doi: 10.1016/j.thromres.2020.04.013. Online ahead of print.
- Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med* 2020 Mar 3;/j/cclm.ahead-of-print/cclm-2020-0198/cclm-2020-0198.xml. doi: 10.1515/cclm-2020-0198. Online ahead of print.
- Maier CL, Truong D, Auld SC, Polly DM, Tanksley CL, Duncan A. COVID-19-associated hyperviscosity: a link between inflammation and thrombophilia? *Lancet* 2020 May 25; S0140-6736(20)31209-5. doi: 10.1016/S0140-6736(20)31209-5. Online ahead of print.
- Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020; **18** (5): 1094–9. doi: 10.1111/jth.14817.

Further information on viscometry and Benson Viscometers is available from Lorna Chun (General Manager). Email: lorna@bensonviscometers.com; Tel: +44 (0)1646 650065

Portable coagulation profiler: proof-of-concept testing and development

Benson Viscometers is developing a novel device that can determine the clotting profile of a blood sample. Furthermore, as this introduction explains, the company also aims to develop the point-of-care capabilities of this device, and also disposables for specialist testing.

Coagulopathy is one of the most preventable causes of death following trauma. It is present at the time of admission to the accident and emergency (A&E) department in 25–35% of trauma patients, and has been implicated as the cause of almost half of haemorrhagic deaths in this group. These patients are associated with higher transfusion requirements, as well as longer stays in intensive care and in hospital generally. In comparison to patients who do not have a coagulopathy, those with it have a three- to four-fold greater risk of mortality, and up to eight times higher mortality within the initial 24 hours of injury.

The correct treatment within the 'golden' first hour following trauma greatly reduces the demand for blood products and also reduces mortality and recovery time. However, blood analysis to ensure correct blood component therapy currently can only be undertaken once the patient arrives at hospital.

Mobile monitoring

In order to reduce the time delay before commencing blood component therapy, Benson Viscometers is in the late stages of developing a mobile coagulation profiler that monitors the clotting of fresh whole blood in real time. This will help healthcare providers determine what type of intervention a patient needs in order promptly to secure 'normal' clotting of the blood, minimise blood loss and avoid unnecessary transfusion of allogeneic donor blood products.

The instrument is small, lightweight, battery-operated and mobile, enabling it to be used at the scene of an incident (eg at the roadside, a major trauma incident or for military use on the battlefield), next to the injured patient (Fig 1) but not connected to them, and in clinical environments such as hospital A&E departments.

The profiler is designed to be always 'ready for use', maintained in a low battery consumption standby mode. It will require no calibration fluids or reagents. There will be no set-up required and therefore it can be operated with minimal personnel training. Insertion

Trauma patients are associated with higher transfusion requirements, as well as longer stays in intensive care and in hospital generally

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Fig 1. The air ambulance is just one environment for which the coagulation profiler is being developed.

of a test capsule automatically activates the analyser ready for the test. Introduction of the fresh blood sample (a 500 µL sample of fresh whole blood is all that is required) by syringe automatically starts the analysis and produces the clotting profile without any further operator actions. An actual blood test coagulation profile is shown in Figure 2.

Graphical display

In order to aid the selection of correct blood component therapy, the coagulation profiler will have algorithms developed to identify normal and frequently encountered abnormal profiles. Test results are displayed graphically in real time with critical patient clotting information, including time to commence clotting, rate of clotting and maximum clot strength. These results are displayed numerically for clarity and there is a grey background plot which is indicative of a normal, healthy clot profile.

Proof-of-concept testing

The profiler has had laboratory proof-of-concept testing where it demonstrated that the system is sensitive to detect abnormalities caused by low platelets, coagulation factor deficiency and for patients on the new direct oral anticoagulants (DOACs) such as rivaroxaban.

After discussions with several clinical teams, the original concept – for use at trauma sites with haemorrhaging patients in both civilian and military environments – has been expanded to include obstetric haemorrhage and the monitoring of patients taking DOACs.

Table 1. Benson Viscometers is developing the coagulation profiler system for use in a range of clinical environments.

Hospital A&E for trauma centres
Ambulances (including air ambulances) for trauma patients prior to and during transport to hospital
Hospital obstetric departments
Hospital neonatal units
Front-line military situations
Field military hospitals
Anticoagulant monitoring in GP practices

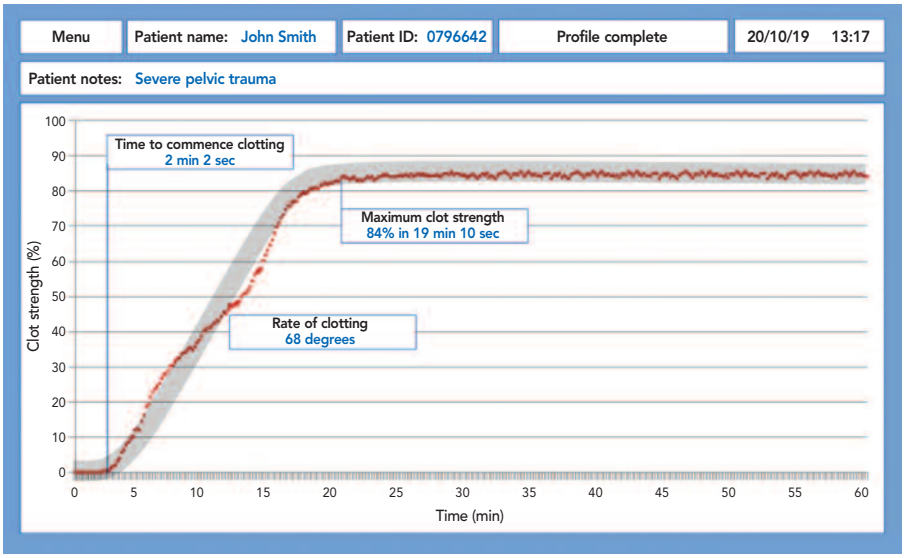

Fig 2. An actual blood test coagulation profile taken and analysed in October 2019.

To aid the selection of correct blood component therapy, the coagulation profiler will have algorithms developed to identify normal and frequently encountered abnormal profiles

Benson Viscometers is therefore currently developing the system for use in a range of clinical environments (Table 1).

The experimental development phase is continuing in order to complete development of the prototype hardware, associated software, peripherals and disposable single-use blood test capsules. The coagulation profiler is designed and being produced to provide a 'step change' improvement to the trauma care pathway.

Several potential areas of future profiler development are under consideration, for development when the core design has been established. These include a solar-powered version for use in developing countries, and disposables with reagents for specialist analysis.

This experimental development phase is required to complete commercial development of the prototype and associated software, peripherals and interfaces, including agreement of the final structure and configuration of the blood capsules.

If successful, this has the potential to offer significant benefits to human health, and the resulting increased turnover would have a transformative effect on the business, directly resulting in new jobs. The contribution to an improved provision of emergency treatment and reduced wastage of critical blood products is likely to provide exceptional benefits, thereby saving money for the NHS.

Patent and partners

Having achieved a European patent covering the Mobile Operating Coagulation Profiler, Benson Viscometers would like to meet potential partners, friends, and those passionate individuals and organisations interested in involvement and sharing in the progress of this project, helping to accelerate the profiler to commercial production.

If you consider this enterprise to be stimulating and exciting, and you have availability or access to vital ingredients – knowledge, expertise, financial resources, development resources, enthusiasm and passion – Benson Viscometers would like to hear from you by email (see address in the company contact details below) in order to assist in bringing this project to fruition.

Benson Viscometers
Unit H – North Estate
Withybush Road
Haverfordwest
Pembrokeshire
SA62 4BS
Tel: +44 (0)1646 650065
Email: profiler@bensonviscometers.com

Potential areas of future development include a solar-powered version for use in developing countries, and disposables with reagents for specialist analysis