

Neuromon bv

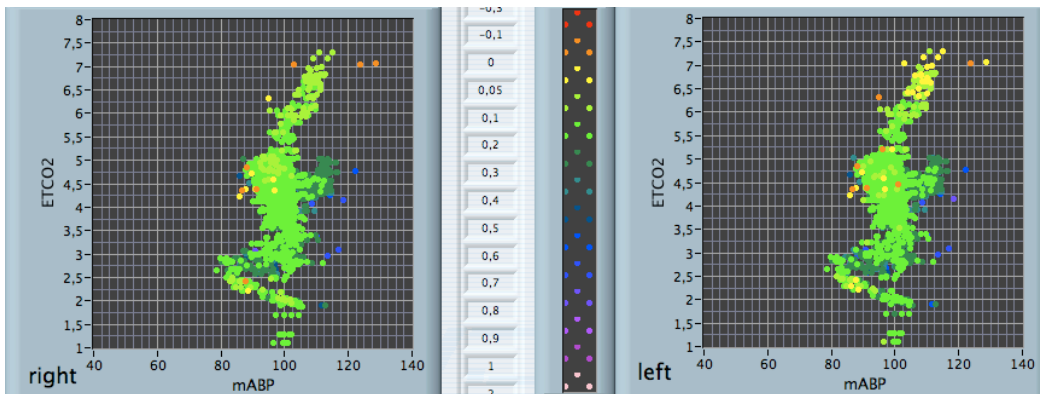
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PaR technology

PaR-technology is a new approach to neurovascular monitoring. From the continuous recording of systemic blood pressure and middle cerebral artery flow velocity a potent parameter is calculated for online monitoring. This so-called pulsatile apparent resistance or PaR expresses the balance between systemic blood pressure and cerebral blood demand.

Every heart beat the PaR parameter is calculated for the left and right hemisphere simultaneously. After color coding, the PaR is plotted as function of the two most important systemic factors determining cerebral hemodynamics, namely the arterial blood pressure (ABP) and the body CO2 content. The latter is derived from the CO2 content in exhalation gas (ETCO2). In this way a map is constructed showing for which combinations of blood pressure and end tidal CO2 the PaR is optimal (green), too low (red) or too high (purple).

Based upon this map a physician is informed immediately (in real time) whether cerebral hemodynamics is disturbed or not. This is essential information in all circumstances that other information about cerebral hemodynamics is lacking, e.g. during the evaluation of a comatose patient in the Emergency Room, or during monitoring of patients in the Intensive Care Unit. Furthermore, Neuromon's integral approach of cerebral hemodynamics, by presenting all information relevant for cerebral hemodynamics on a single screen is highly suitable for (patho-)physiological studies of cerebral hemodynamics, e.g. in the autonomic function lab. or during tests of pharmacological agents with effects on brain circulation.

Some characteristics:

- combines TCD, ECG, ETCO2 and ABP signals
- calculates a blood pressure corrected pulsatility index
- detects the limits of cerebral autoregulation
- detects increased intracranial pressure
- integrates multimodal information crucial for cerebral hemodynamics

The PaR-parameter in more detail

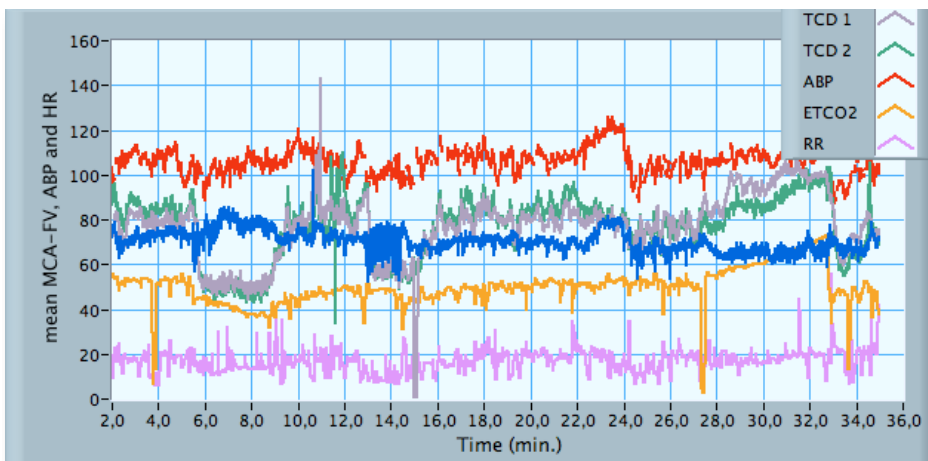
The blood hemodynamics in the brain is characterized by blood-pressure and blood-flow. The relation between these two is non-linear. The blood vessels play an active role by constriction and dilatation continuously altering the relation between blood flow and blood pressure.

The PaR parameter is based upon the innovative notion that these changes not only occur on a somewhat larger time scale (e.g. tens of seconds to minutes) but that vaso-constriction may also occur within the time frame of a single heart beat. By contracting during systole the major arteries establish a peristaltic wave that contributes to the pressure wave and allows it to penetrate into remote capillary networks. This response of the blood vessels can be influenced by many factors and when disturbed can lead to catastrophic results for the brain.

To explain how this pulsatile vaso-constriction alters the relationship between blood pressure and blood flow Neuromon has developed a computer model simulating this interaction in major cerebral arteries and explaining its non-linearity. The model demonstrates how the PaR parameter detects different (patho-)physiological conditions.

The PaR parameter at work - two examples

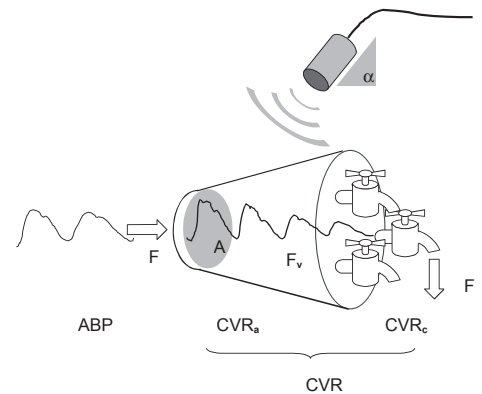
The PaR parameter is defined in a unit-free space, making it robust and highly suitable for inter-individual comparison. When low values of the PaR are encountered (<0) this indicates dependence on collateral flow due to a major obstruction within a feeding artery to the brain. This is nicely illustrated by the following patient:



A 52 year old woman was evaluated for a history of 20 years of suddenly occurring loss of consciousness. Over these years the patient had undergone many investigations, amongst which electro-encephalography, electro-cardiography, echo-sonography of the heart, implantation of a so called reveal pacemaker, etc. excluding common causes for loss of consciousness such as epilepsy, disturbances of heart rhythm, etc. Finally, she was sent in for autonomic function testing. The results of autonomic testing are shown in the graph above. All responses fell within the normal range. No important

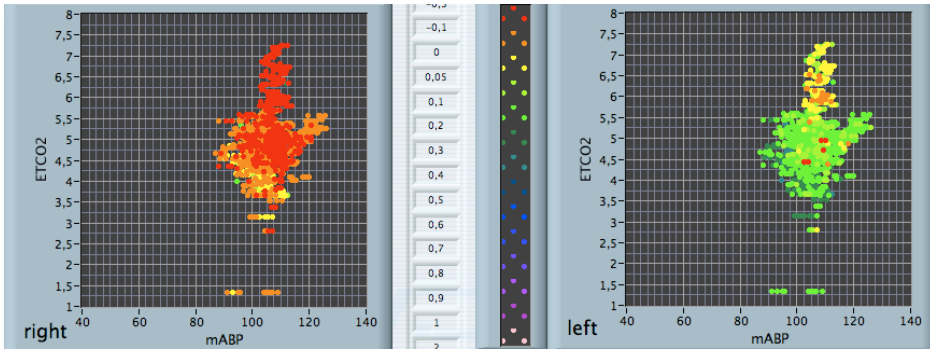
PaR-technology:

an innovative approach to neurovascular monitoring



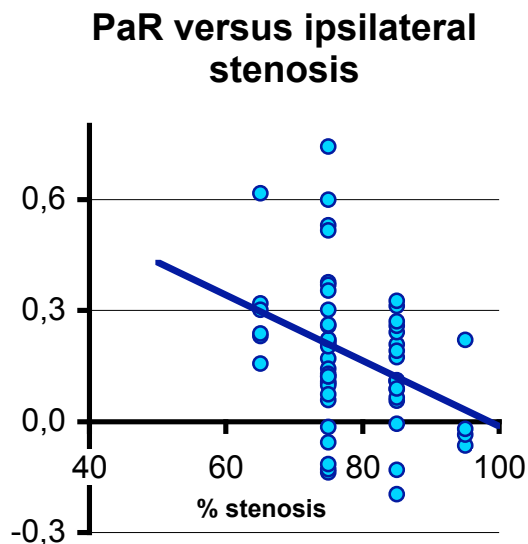
differences were seen between the mean flow velocities over the left and right middle cerebral artery (graphed as TCD1 and TCD2).

However, when the PaR parameter was analyzed for both hemispheres independently we found the following:



Such asymmetry is very uncommon (see graph at the top) and has so far only been encountered in patients with a severe stenosis of one of the major feeding arteries to the brain. Based upon the asymmetry in the PaR the patient underwent ancillary investigations which revealed a major obstruction in the a. anonyma on the right side. By stenting the patient finally became symptom free after suffering 20 years of recurrent episodes of loss of consciousness.

The previous example shows how the PaR parameter can be utilized in individual patients. The following example shows how individuals with abnormalities can be identified within a group.



In the Martini Hospital Groningen patients prepared for carotid artery surgery have been studied extensively making use of PaR technology. The PaR parameter can stratify patients according to the hemodynamic consequences of a stenosis (see above).

These consequences are often limited since there are abundant collateral pathways

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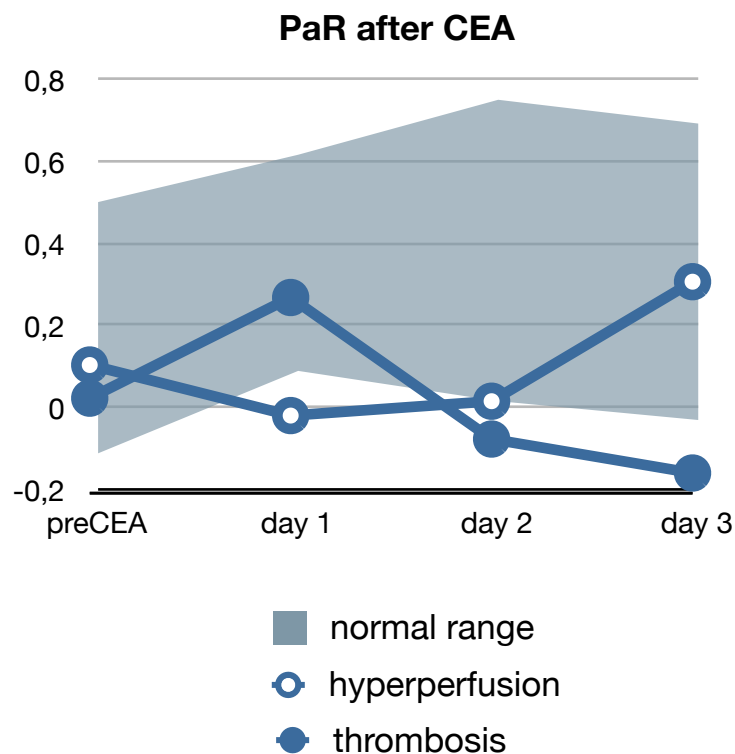
Neuromon BV is supported by a grant from the Province of Groningen and the European Fund for Regional Development (EFRO) as part of the Innovative Action Programme Groningen (IAG).



within the cranium, allowing blood to bypass the stenosis, for instance by left-right shunting. In addition the PaR parameter can be used for follow-up during the first three postoperative days. This is demonstrated by the following example.

A series of nearly 50 patients undergoing carotid endarterectomy was studied by means of PaR technology. Three patients suffered complications: one patient experienced a temporary hyperperfusion in the hemisphere above the carotid artery operated upon, in one patient an early thrombosis occurred in the operated carotid and one patient suffered a minor stroke due to thrombo-embolism presumably during surgery.

Two of the three patients were identified by daily postoperative measurement of the PaR because their follow up clearly deviated from the normal picture as demonstrated by the graph below:



In the patient with temporary hyperperfusion the abnormally low PaR parameter was caused by central hypoventilation occasionally occurring post-operatively and was accompanied by high intracranial flow velocities on the side of surgery. By actively supporting breathing on the ICU the patients condition improved, the PaR values normalized and the patient could be dismissed without further complications.

In the patient with the early thrombosis the PaR parameter identified the moment during follow up that this occurred, namely between the measurements on day 1 and day 2. In future, a sudden decrease in PaR during follow-up may be taken as indication for re-exploration: a fresh thrombus can often easily be removed by suction of the re-opened vessel. Luckily, this early occlusion did not cause neurological deterioration in this particular patient, but in other cases re-exploration may be crucial to prevent further ischemic injury to the brain.

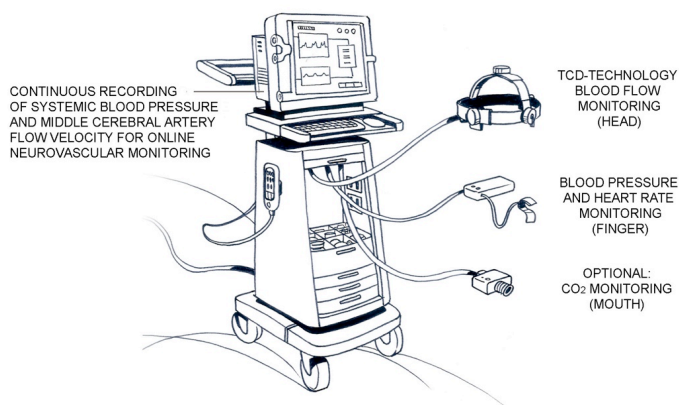
So, the PaR value is capable of detecting abnormal cerebral hemodynamics within the individual patient. The PaR value provides the earliest possible warning for hemodynamic instability within the brain, otherwise only detectable with substantial time delay by for instance MR-scanning, which is not preferred for patients in the Intensive Care Unit.

Ongoing Research

Clinical studies have shown positive results in detecting single side arterial occlusion or stenosis (300 patients). The PaR parameter can be assessed non-invasively and this makes it highly suitable for application in a wide range of patients in whom cerebral perfusion is at stake. For instance, in the Erasmus Medical Center Rotterdam PaR-technology is tested in pregnant women at risk for developing eclampsia: an important complication of pregnancy that threatens the life of mother and child. Further research involves the study of changes in PaR following a subarachnoid hemorrhage: a major bleeding within the (subarachnoid) space surrounding the brain which is well known for potentially life-threatening complications. This study is performed in close cooperation with the University Medical Center Groningen.

Preliminary results have recently been presented during the 13th Meeting of the European Society for Neurosonology and Cerebral Hemodynamics May 2008 in Genova Italy. The PaR technology was accepted as a novel and promising technique for the description of intracranial hemodynamics in health and disease.

NEUROMON PaR TECHNOLOGY SYSTEM



Future plans

Future plans involve the development of an integral neurovascular monitoring system, bringing these different modalities together within a single housing. For this purpose, Neuromon collaborates with BMEYE BV, Amsterdam, a producer of non-invasive blood pressure measurement equipment, and Rimed Ltd. Raanana Israel, a producer of transcranial Doppler systems. The expected synergism and innovative capabilities of this collaboration is enormous. For instance, plans have been made to develop an operator-independent TCD system that would greatly enhance the applicability of PaR technology on the ICU and in the ER.



Facilitated by the Province of Groningen and the European Fund for Regional Development (EFRO) as part of the Innovative Action Programme Groningen.



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'PaR Technology' project

The 'PaR technology' project is initiated by Neuromon B.V. in close collaboration with BMEYE B.V. and Rimed Ltd. It has recently received the prestigious Eureka label and is supported by a SI02 grant from the European Union.

