innovating medical technology

in.nrw

patient customized engineering in aachen

PaCE – Patient Customized Engineering

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Investition in unsere Zukunft
Europäischer Fonds
für regionale Entwicklung

Ministerium für Innovation,
Wissenschaft und Forschung
des Landes Nordrhein-Westfalen

Ziel2.NRW
Regionale Wettbewerbsfähigkeit und Beschäftigung

Ladies and Gentlemen,

As research trends move towards the use of personalized medicine, many projects are focused on genetic, molecular, biological and pharmacological approaches. The aim of personalized medicine is to analyze and image patient-related biological processes at the cellular and molecular level and use the information provided to influence these processes therapeutically.

Personalization strategies and a correspondingly improved patient orientation also present major opportunities relative to the field of medical engineering.

This is where the Aachen-based medical engineering network ***innovating medical technology in.nrw*** *comes in: True to the guiding principle,* ***"Patient Customized Engineering"****, customized solutions and therapies adapted to specific diseases and problems of the individual patients are being developed.*

The development of medical components, devices and systems "tailored" to an individual pathological requirement in a specific patient is carried out more so at the anatomical and physiological level than at the pharmacological level. There is an enormous amount of untapped potential for improvement of interaction between technical systems and recipient organisms.

Based on this idea, a total of six R&D projects in combination with 40 partners in the Aachen-based network are completing the research and development of a new generation of medical devices and systems. These projects have a focus on the particularly relevant field of cardiovascular disease which is still the leading cause of death in Germany. Research and development within this field also represents a particular scientific and economic advantage in the Aachen region.

We are convinced that "Patient Customized Engineering" represents a significant optimization strategy with high levels of innovation and is moving in the direction of improved patient care.
We are glad to serve as your contact.

Sincerely,

Prof. Dr. Thomas Schmitz-Rode
Speaker of the Consortium
"innovating medical technology"

Dear Reader,

Personalized healthcare and medical engineering is one of the key areas of health research. Population ageing – the demographic change – calls for innovative and patient-focussed medical care, which must be both effective and efficient.
We refer to this as Patient Customized Engineering, and it has huge potential that we are eager to tap into. Already today, North Rhine-Westphalia can boast a large concentration of research institutions and businesses with activities in and around medical technology. Our state is therefore in an excellent place to continue coming up with innovative and technological advances that are sustainable and focussed and thus in line with our research strategy, which is called 'Progress NRW'.
These advances'made in NRW' aim at technological change as well as social progress. We are funding application-led research because we believe that technological advances should mean innovation that people benefit of.
The projects of the biomedical engineering network, 'innovating medical technology in.nrw', with their focus on cardiovascular disease, make great strides in implementing this. By launching our InnoMeT. NRW competition, we are going all out to support this key area of healthcare research in a joint effort with the cluster 'MedizinTechnik.NRW'.
This brochure is designed to enable the expert community and a wider audience to keep track of developments in this field of interest. I am following this process with keen interest and wish the scientists and researchers continued success.

Svenja Schulze
Minister for Innovation, Science and Research of the State of North Rhine-Westphalia

Patient Customized Engineering

Medical technology is a multidisciplinary research area into which new knowledge is continuously flowing from the relevant fields of medicine, engineering, information technology and the natural sciences. The development of constantly new application fields is leading to a growing importance of this discipline. Today, with regard to innovations in medical technology, the individualization of medicine is also setting the pace besides other "progress dimensions" of computerization, miniaturization and molecularization. This type of individualized, i.e. personalized or patient-customized medical technology is distinguished by the fact that medical products are tailored to the anatomical, physiological and, in part, also cellular particularities of the individual patient. Hereby it deals with an optimization strategy harboring enormous potential and whose aim is to improve diagnostic and therapeutic properties of medical products and, at the same time, is based on technological advances that have become established in the past two decades. Among these advances, for example, are an energy-efficient microsystem- and sensor technology for autarkic applications or developments in such thematic areas as nanotechnology and tissue engineering. The individualization of medical products or instruments can enable a safe and less invasive application as well as an efficient molding of technology that would not be possible in classical medical technology. The personalization is already penetrating various highly innovative areas of medical technology such as imaging diagonostics. Primarily in the fields of magnetic resonance imaging (MRI) and positron emission tomography (PET), specific biomarkers are added to the applied contrast agents or radiopharmaceuticals in order to visualize patient-specific target structures and thereby bolster the performance of the imaging technique. Today, for example, the smallest metabolic changes can be visualized by imaging methods or by a combination thereof so that e.g. tumor metastases can be detected early on. Imagining techniques are also applied in the production of individualized prostheses. Here, MRI and computer tomography (CT) data serve as the basis for the manufacture and individual fitting of joint endoprostheses. Moreover, imaging is playing an increasing role in surgical interventions. In particular, for minimally invasive procedures, incorporating imaging techniques is contributing to making such surgeries shorter, less invasive and more precise and individualized. Furthermore, personalization concepts are increasingly being followed regarding medical implants. The newest generation of implants contains either biological components, is completely manufactured from biomaterial, or is covered with bio-functionalized surfaces. Autologous cells or tissue are often used for producing such bio-implants, thereby leading to the highest possible degree of individualization. A clear advantage of this strategy is the great biocompatibility that inherently results in improved immunological properties and, thus, ensures the high long-term stability of the bio-implants.

There is also an increasing personalization in the so-called 'intelligent' implants or also theranostic implants, such as implantable pressure sensors for monitoring chronic heart failure. Such implants are capable of specifically determining medical parameters and immediately initiating implant-communicated therapy measures.

The aforementioned examples show that personalization has already advanced and will continue to gain importance in the field of medical technology. An individualization of diagnostic and therapy methods will contribute to make these techniques less invasive and more effective and finally will help to considerably save costs in the healthcare system. The possible higher costs incurred by producing patient-customized medical products are more than offset by savings through shorter operation times and in-patient treatment times as well as by more effective and sustainable therapy possibilities, which altogether, from a healthcare economic perspective, confers a clear advantage over classical medical technology.

Yet an interdisciplinary cooperation among engineers of various academic disciplines, natural scientists and medical doctors is indispensible for the development of innovative medical products. Aachen, as a center of academia and industry, has always stood out in this regard. In particular, in the field of medical technology, the region of Aachen counts as one of the leading regions in Germany – a progress reflected by the fact that large R&D projects could be constantly realized in the field of medical technology in Aachen by means of industrial and public funding. The joint project "in.nrw-innovating medical technology" assumes here a clear special position. On the one hand, four of the six future focal themes of medical technology, recommended in a study of the German Federal Ministry for Education and Research (BMBF)[1], are being handled:

1. Functional and cell-biological imaging;
2. Minimally invasive surgery and intervention;
3. e-Health, telemedicine, networking; and
4. Medical technology for regenerative medicine.

On the other hand, the components of the individualization of medical technology are explicitly integrated, since here patient-customized solutions are being developed for cardiovascular therapy.

1 Farkas, R., Becks, T. et al. (2005): Zur Situation der Medizintechnik in Deutschland im internationalen Vergleich. Study commissioned by the BMBF, p. 730.

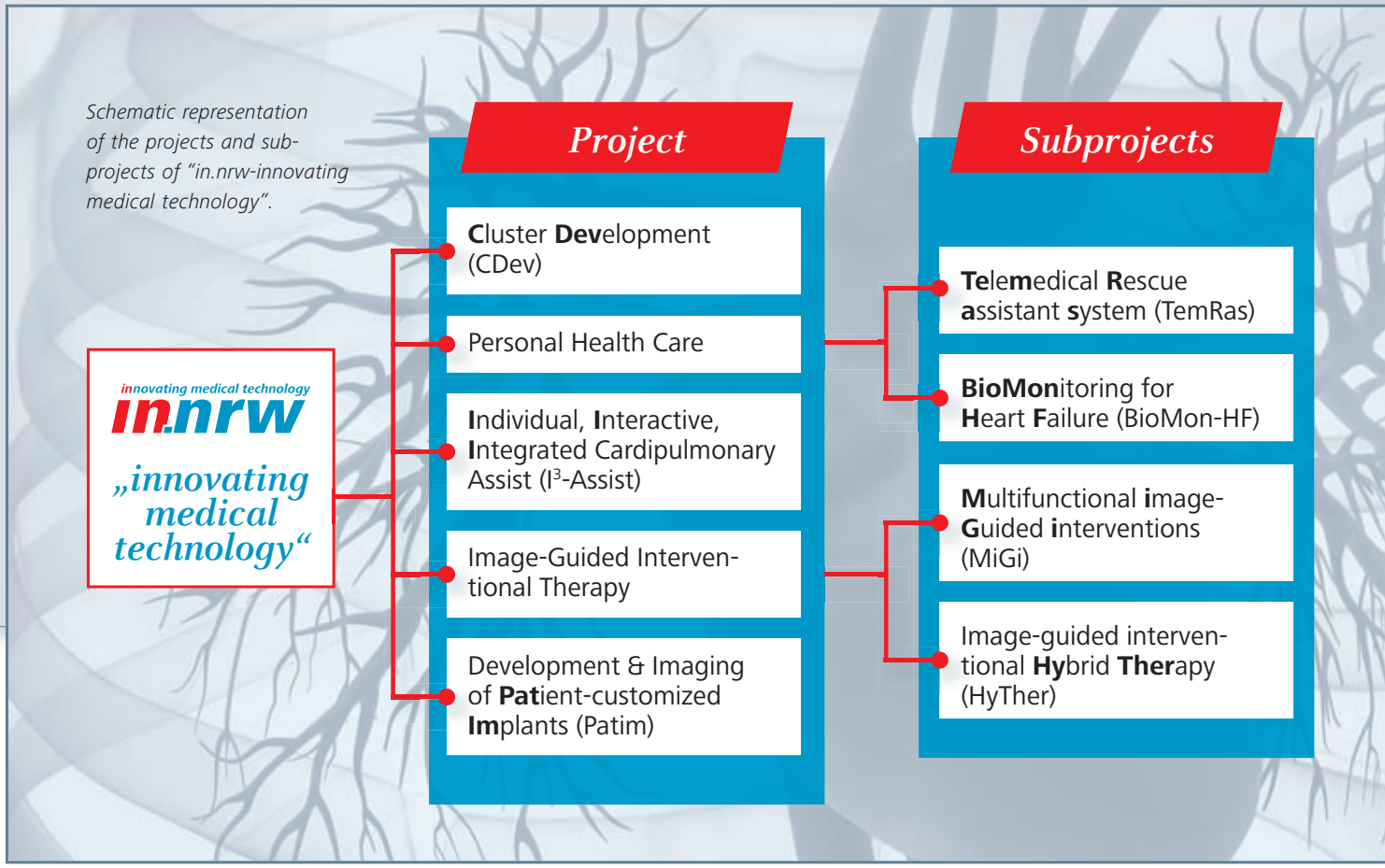
Aachen's R&D projects in patient-customized medical technology

The enormous economic and therapeutic potential of "patient-customized medical technology" was already recognized in Aachen early on and could be pushed by the massive support of the Ministry for Innovation, Science and Research of the state of North Rhine-Westphalia (MIWF) and of the EU (European Fund for Regional Development) within the research cluster "in.nrw-innovating medical technology".

The central aim of the cluster "medtec-in.nrw" is to develop a new generation of biomedical instruments and systems for innovative patient-customized medical- engineered solutions in cardiovascular therapy. Within the scope of six R&D projects, various methods will be optimized and further developed for treating patients with cardiovascular illnesses. Here, the constant primary aim is the fitting of methods and products to the specific pathological condition and needs of a patient towards acquiring the optimal care of each particular patient. The following scheme outlines the structure of the projects and subprojects of "in.nrw-innovating medical technology."

The following sections will closer introduce some of the subprojects of the research cluster "in.nrw-innovating medical technology" in order to exemplify and elucidate the huge potential of patient-customized medical technology – the key technology towards ensuring a sustainable and economical medical healthcare system of the future.

Schematic representation of the projects and subprojects of "in.nrw-innovating medical technology".



Biomon-HF

innovating medical technology in.nrw patient customized engineering in aachen

"Not losing sight of heart failure in the nightime, too"

Congestive heart failure is a chronic disease showing the highest mortality with age, i.e., with a prevalence of 5-10% in individuals 65 years and older. Because primarily a monocausal and healing therapy is rarely possible, the treatment options are often confined to prevention of complications (palliation). An essential role is thus played by diagnosis and treatment of accompanying diseases (comorbidities). In addition, early detection of an exacerbation of the disease plays a similarly central role. The care and support of affected patients, especially in rural areas, is increasingly difficult because of the rising shortage of primary care physicians. Against this background, researchers from Aachen, Germany, have set themselves the goal of advancing development of individualized, nightly telemonitoring leading to out-patient care for cardiac insufficiency. External sensors ought to improve the early detection of concomitant diseases as well as the timely diagnosis of a worsening of heart failure. The scientists make use of the nocturnal sleep period in humans, approximately 30% of the day, to more intensively monitor the patient's vital signs at home, which is more comfortable for the patient. The sleep phase is characterized by a stable, relatively sedentary measurement period that optimizes sensor signal quality. Through the remote monitoring of patients, there is an enormous cost-savings potential from avoiding preventable emergencies and, thus, relieving medical staff.

Within the framework of the project and for early detection of concomitant diseases in heart failure, sensor concepts for future home use have been utilized for the first time clinically in feasibility studies to gain measurement data for algorithm development. The addressed concomitant diseases are sleep apnoea, high blood pressure, arrhythmias and edema. The investigated sensor solutions are supposed to allow for individualized telemonitoring in heart failure patients with comorbidities and early recognition of a worsening of the heart failure.

A special challenge for the project was to define five clinical studies for generating measurement data with the sensor concepts investigated in the project and to successfully conduct these clinical studies within the project period. All the studies were subjected to ethical and legal evaluation and were approved by the Ethics Committee of the University Hospital Aachen. The studies are currently being executed under the direction of Prof. Dr. med Patrick Schauerte, PD Dr. med. Johannes Schiefer and Dr. med. Matthias Zink at the University Hospital Aachen.

An "Electronic Data Capture (EDC)" platform with "electronic case report forms (eCRF)" has been developed in the project and allows an optimized, time-efficient and real-time recording of clinical reference measurements together with measurements from the investigated sensor concepts for the study workflow.

Based on the study data collected up to current project status, first algorithms have been developed to detect the concomitant diseases and worsening of cardiac insufficiency. It has been

Partners:

- **Philips Technologie GmbH Research Laboratories**
  Thomas Vollmer
  e-mail: thomas.vollmer@philips.com
- **Philips Chair for Medical Information Technology (MedIT)**
  Univ.-Prof. Dr.-Ing. Dr. med. Steffen Leonhardt
  e-mail: medit@hia.rwth-aachen.de
- **Department of Cardiology, Pneumology, Angiology and Intensive Care (Internal Medicine I)**
  Prof. Dr. med. Patrick Schauerte
  e-mail: pschauerte@ukaachen.de
- **I.E.M.GmbH**
  Olaf Steffens
  e-mail: o.steffens@iem.de
- **Forschungszentrum Jülich – Electronic Systems (ZEA-2)**
  Dr. Michael Schiek
  e-mail: m.schiek@fz-juelich.de
- **Takeda Pharma GmbH**
  Dr. Gerhard Kiel
  e-mail: Gerhard.Kiel@Takeda.de

shown that algorithms for the detection of atrial fibrillation can be developed based on time-frequency analysis of the measurement data from the intelligent bed. It is also possible to reliably determine respiratory and heart activity from the measured data of the intelligent bed.

In animal studies, the achievable accuracy in measuring edema, based on bioimpedance measurements, could be evaluated. Moreover, the influence of fluid retention on the measurement of hemodynamic parameters of the heart could be shown by means of impedance cardiography.

It has been demonstrated that the in-ear photoplethysmography (PPG) sensor can measure heart rate and arterial oxygen saturation (SpO_2) in good agreement with the gold standard. Sleep apnoeas can also be readily detected.

On the basis of the clinical study data collected and the biosignals measured with the sensor concepts, robust algorithms are being developed by the project partners for recognizing the concomitant diseases addressed in the project and the worsening of the chronic heart failure. For nocturnal biomonitoring at home, the sensor and algorithmic concepts showing best sensitivity and maximum specificity are being selected.

In the further course of the project, improved algorithms are to be developed, e.g. for detecting sleep apnoeas from intelligent bed measurement data. The performance of algorithms is to be evaluated with additional study data records. The efficiency of the concepts is to be further enhanced and optimized by combining algorithms.

Modelling and simulation methods from the field of "computational engineering science" are to be used for the patient adaptation of the investigated sensor solutions. To extract morphological information, a special role is to be played by imaging-based diagnostic procedures. There is a desire to establish appropriate partnerships with experts in these disciplines. Moreover, cooperations in the fields of e-health and telemedicine are intended. Clinical cooperation partners in cardiology, pulmonology and sleep science are being sought for clinical trials within the scope of feasibility studies.

Guest Commentary

Günter von Aalst
Director, Representation of Techniker Krankenkasse in North Rhine-Westphalia

Personalising diagnostics and therapy can be viewed as a significant optimisation strategy that increasingly gains importance in medical engineering. From the angle of medical engineering, a human's individuality is expressed on the anatomical, physiological and, to some extent, also on the cellular level. It should be possible to map the effectiveness and efficiency of patient customised engineering in cost-benefit analyses. In my opinion, contributions to more patient safety would be particularly desirable.

"Ensurance of emergency medical care through telemedicine"

The application of telemedicine to ensure high-quality emergency care is becoming increasingly important against a background of increased usage in emergency medicine with resource shortages and resulting greatly increased journey times, particularly in rural areas. Therefore, TemRas (Telemedical Rescue Assistant System) has assumed the task of meeting these challenges with an innovative concept to improve quality of emergency care. Emergency medical expertise has to be applied where it is really needed. The aim of the three-year project is to introduce a tele-EMS physician who supports the rescue teams on site from a teleconsultation center by using vital signs as well as sound and image transmission from the emergency site.

Whereas the previous project Med-on-@ix (2007-2010 SimoBIT Grant Programme of the Fed. Ger. Ministry for Economy and Technology (Bundesministerium für Wirtschaft und Technologie (BMWi)) demonstrated the feasibility of the telemedical rescue assistance system, TemRas has enhanced the consultation system in terms of widespread use. The basic framework to ensure a comprehensive, time- and location-independent availability of emergency medical competence is formed by:

1. establishing a teleconsultation center in Aachen;
2. the telematic conversion and equipping of six ambulances;
3. the miniaturization of the portable transmission unit; and
4. the IT modular networking of components.

The expected challenges have been met with an easy-to-use system that safely and securely transmits medical data even in rural areas – with limited mobile wireless connections – and a comprehensive organizational approach to implement the system in the emergency rescue service. Further development of the existing components and integration of essential interfaces to other components ensure the degree of innovation of this approach as well as an optimized information- and database for the telemedical assistance in emergency care.

Since August 2012, the system is being subjected to a one-year evaluation in five NRW rescue service areas (Aachen, Düren, Euskirchen, Heinsberg, and Cologne). The rescue team on site decides alone if and when the tele-EMS physician should be consulted.The rescue team is supposed to consult the tele-EMS physician in situations where an emergency physician had already been alarmed but is still on the way or even is involved in another case. Up to now, about 180 medical consultations have taken place, whereby no serious technical problems nor serious adverse events have occurred. Based on current guidelines of emergency medicine, the administration of a number of medications and measures has been delegated successfully by the tele-EMS physician to the emergency personnel on site, enabling fast and highly qualified individual patient treatment. One example is as follows:

A rescue team is called to a vague emergency and finds a 42-year-old man complaining about dizziness, drowsiness and pressure in the chest. The patient appears pale, with cold sweat and a high blood pressure with increased heart rate. An emergency physician is alarmed immediately, and the patient is transferred to the ambulance. Parallel to this, the paramedics contact the tele-EMS physician and describe the situation. The tele-EMS physician then calls for a 12*-lead ECG and observes the patient via the video camera in the ambulance. After a thorough examination of the data, the tele-EMS physician delegates the administration of various medications to stabilize the patient. A short time later, the emergency physician arrives on the scene and takes measures to further stabilize the patient and prepare him for transport while the tele-EMS physician informs the catheter laboratory.*

Besides consulting on site, the tele-EMS physician is responsible for relaying comprehensive prior information about the condition of the patient to the hospital for further treatment, either digitally or in a personal conversation. The teleconsultation center serves as an information hub to optimize the flow of information at the interface between the emergency rescue service and the hospital, in order to increase the quality of the entire emergency care.

Already now, there are efforts to establish the system – after funding has terminated – in regular emergency medical services in NRW to improve both the quality and efficiency of emergency medical services and to effectively utilize the 'resource', emergency physician. The continuation of the research on sustainable establishment of telemedicine in emergency medical services also carries considerable potential for testing innovative medical devices in emergency medical services.

Guest Commentary

Mr. Rudolf Henke
President, North Rhine Medical Association

Personalized medicine is currently considered a source of great hope in the medical field. Specific therapies adapted to the individual also include treatment individual prostheses and implants, as well as imaging techniques and telemedical applications. The Aachen region, a leader in modern medical engineering with its interdisciplinary R&D network, functions as a pacemaker in the development of patient-adapted solutions for cardiovascular therapy. Treatment by a physician is always an individual patient-oriented process per se. The increasing personalization of resources results in new challenges to the physician-patient relationship with a framework of scientific progress, increased information requirements and more patient involvement.

Partners:

- **Institute Cluster IMA/ZLW & IfU RWTH Aachen University**
  Christian Büscher
  e-mail: christian.buescher@ima-zlw-ifu.rwth-aachen.de
- **Department of Anaesthesiology, University Hospital Aachen (UKA)**
  Dr. Jörg Brockmann
  e-mail: jbrokmann@ukaachen.de
- **P3 Communications GmbH**
  Tadeusz Brodziak
  e-mail: tadeusz.brodziak@p3-group.com
- **3M Medica**
  Oliver Wiegand
  e-mail: owiegand@mmm.com
- **Philips Healthcare Germany GmbH**
  Thomas Groß
  e-mail: thomas.gross@philips.com

innovating medical technology

MiGi in.nrw patient customized engineering in aachen

"Foregoing x-ray screening on hand of new operation tools"

Minimally invasive endovascular interventions are currently being performed under continuous X-ray control and application of contrast agents into the vascular system. Hereby, the surgical tools are positioned in the vascular system with the help of guide wires.

The type of application but also the patient-specific morphological characteristics lead to different requirements of the guide wire with respect to its size and mechanical properties. The structures surrounding the vessel, and often the target structure itself (e.g. a tumor), can only be imaged with this method either indirectly or not at all.

Magnetic resonance imaging (MRI) provides a way to visualize not only the vessels but also the surrounding soft tissue with high spatial resolution and very good contrast. As this procedure completely dispenses with potentially harmful x-ray radiation, it is clearly superior to the currently applied standard procedure in terms of the health of patients and medical staff.

Long, electrically conductive materials, such as conventional guide wires, may not only cause MRI artifacts but may also "couple" with electromagnetic fields and thus bundle energy at their tips, which poses a serious danger to both patient and physician.

Therefore, the aim of the MiGi (**M**ultifunctional **i**mage-**G**uided **i**ntervention) project is to develop flexible production technologies for manufacturing novel MRI-safe guide wires from fiber-reinforced plastics. The new guide wires are free of metallic components and are manufactured with tailor-made materials whose properties are adapted over the entire length of the wire. They are designed to meet the requirements of MRI, x-ray radiography and ultrasound in terms of visibility and patient safety. Miniaturization of the wire cross-section presents a further challenge.

To realize the project, the Fraunhofer Institute for Production Technology (IPT) has developed a new production technology for micro-profiles made of fiber-reinforced plastics. By using the so-called micro-pullwinding process, profiles of fiber-reinforced plastics with diameters of a few hundred microns can be produced; these serve as the basic body of the guide wire. The mechanical properties of the profiles can be adapted in the continuous manufacturing process so as to adjust bending- and torsional stiffness in a targeted manner. Modification of the mechanical properties can be realized continuously during the production process, so that customized product properties are achieved in mass-production processes. In subsequent process steps, the project partner Nano4Imaging GmbH will apply markers onto the profiles, whereby the markers are exactly fitted to the intended intervention for imaging of the guide wires, before they are coated with a hydrogel by Hemoteq AG, another project partner.

Using this process chain, it is now possible for the first time worldwide to produce innovative guide wires with unique, so-called "Tailored Mechanical Properties" (TMP) for use in multi-functional imaging procedures in a mass-production-compatible process that can also be accurately adapted to specific interventions in individual patients. Moreover, defined adaptation of the mechanical properties online during the production process can render unnecessary the additional assembly and processing steps required to date in production of guide wires with flexible tips.

Due to the specific features of MRI, special requirements also apply to safety measures during MRI examinations and to imaging properties of the guide wire. Within the framework of the project, various markers, marker concentrations and distances as well as real-time, indirect and direct angiography sequences have been developed and tested in phantom models to facilitate an optimized, highly time-resolved control and visualization of the guide wire in MRI. Not only should the guide wire be readily visible and applicable in MRI, but it should also be possible to switch to different radiological imaging methods (MRI, x-ray, CT, ultrasound) during an intervention without significant interruptions. The objective here is to ensure an optimal individualized patient care.

Guest Commentary

Dr. med. Holger Gothe
M.A. Institute Deputy Director Institute of Public Health, Medical Decision-Making and Health Technology Assessment UMIT – University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria

Provider and payers argue about whether personalized medicine leads to an explosion of healthcare costs. If profit expectations are dampened for personalized therapeutics due to regulatory measures, personalized diagnostics could help providers compensate for the lost profits. Patient customized engineering therefore requires an enormous amount of study focussed on the relevant healthcare economics to determine what costs effects are actually to be expected.

Partners:

- **Department of Diagnostic and Interventional Radiology, University Hospital Aachen (UKA)**
  Dr. Nils A. Krämer
  e-mail: kraemer@rad.rwth-aachen.de

- **Fraunhofer Institute for Production Technology IPT**
  Dr. Michael Emonts
  e-mail: michael.emonts@ipt.fraunhofer.de

- **Hemoteq AG**
  Dr. Matthias von Walter
  e-mail: hemoteq@hemoteq.de

- **Nano4Imaging GmbH**
  Prof. Dr. Paul Borm
  e-mail: paul.borm@nano4imaging.com

HyTher innovating medical technology in.nrw patient customized engineering in aachen

"Intelligent multi-sensor system enables individualized implantation of vascular prostheses"

Minimally invasive, image-guided therapies are becoming increasingly important, in particular, for endovascular therapy. Especially for patients who would not survive surgical treatment due to comorbidities, various interventional therapies have been developed and have established themselves as therapeutic standards in a large number of cases over time due to of their less traumatic approach (e.g. PTA, percutaneous transluminal angioplasty; stent angioplasty; TIPSS, transjugular intrahepatic portosystemic stent shunt).

The project HyTher aims to improve the precision and safety of complex image-guided interventional therapeutic procedures while minimizing radiation exposure. The goal is to develop a hybrid intervention technique by developing and integrating advanced imaging, registration and navigation technologies as well as knowledge-based, patient-customized 3D models.

One example of the use of image-based minimally invasive treatment procedures is the interventional treatment of large aortic aneurysms, a significant disease with about 200,000 new cases in the United States alone and potentially life-threatening complications (e.g. rupture of the aorta). Minimally invasive repair of the aorta from the inside of the vessel outwards (EVAR) represents a much less traumatic method than the complex procedure of open aortic replacement. Recent studies have confirmed better postoperative outcomes for EVAR than for open surgery, namely a post-operative 30-day mortality of 4.3% after open surgery vs. 1.8% after EVAR[1].

However, a major problem with the endovascular procedure is the fact that the anatomy of the vascular tree and the location of the junctions vary from person to person. While it is possible to customize prostheses for aneurysms involving these vessels, this involves a significant time delay of up to eight weeks, during which time a significant number of these patients die.

An intra-interventional, image-guided antegrade fenestration of the prosthesis at the level of the vascular branches represents an option that has not yet been developed thoroughly and is addressed in this project.

The HyTher project now uses a novel approach: Electromagnetic tracking allows for localization and tracking of an instrument on the basis of CT sectional image data recorded in advance. The latest developments now enable the integration of the coils in the tip of the instrument, permitting tracking of the instrument tip in the image data record (tip tracking) in real time during the intervention.

1 LC Brown et al.; The UK EVAR trials: randomized trials of EVAR vs. standard therapy, 02-2012

Partners:

- **Department of Diagnostic and Interventional Radiology, University Hospital Aachen (UKA)**
  Univ.-Prof. Dr. Christiane Kuhl
  e-mail: ckuhl@ukaachen.de
  Dr. med. Peter Isfort
  e-mail: isfort@ukaachen.de
- **Chair of Medical Engineering (mediTEC), Helmholtz-Institute for Biomedical Engineering, RWTH Aachen University**
  Univ.-Prof. Dr. Klaus Radermacher
  e-mail: radermacher@hia.rwth-aachen.de
- **Institute of Applied Medical Engineering (AME), RWTH Aachen University**
  Univ.-Prof. Dr. Catherine Disselhorst-Klug
  e-mail: disselhorst-klug@hia.rwth-aachen.de
- **SurgiTAIX AG**
  Dipl.-Ing. Holger Weber
  e-mail: portheine@surgitaix.de
- **Vygon GmbH & Co KG**
  Dipl.-Ing. Ralf Quentin
  e-mail: ralf.quentin@vygon.de

These technologies were adapted to the requirements of complex endovascular applications within our project through the development of a dedicated image- and model-based navigation platform and the production of prototypes of electromagnetically navigable guide wires and guided catheters. Hardware and software solutions were also developed for reliable registration of CT data to compensate for the continuous breathing movement of the patient. For this purpose, a prototype in the form of an intelligent Multi-Sensor System (iMSS) was designed that reliably records both the respiratory cycle and the respiratory mode (proportion of abdominal and thoracic respiration).

Phantom experiments could demonstrate that the developed (guided catheter, guide wire, navigation software, iMSS) enable a reproducibly reliable, antegrade in situ fenestration of aortic prostheses. This procedure was then carried over to an initial animal experiment in which the antegrade in situ fenestration of an aortic prosthesis was realized successfully under electromagnetic tracking with subsequent stent implantation in both renal arteries in a worldwide first attempt. This allows a fitting of the prostheses at the highest level, namely within the body by taking into account the individual anatomical conditions.

In the further course of the project, these components will be further optimized in order to transfer the technology to other endovascular interventions. Thus, the project is also focussing on a second procedure: creating an artificial vascular channel between the portal and hepatic venous systems by implanting a so-called Transjugular Intrahepatic Portosystemic Stent Shunt (TIPSS). This complex intervention also often involves considerable difficulties and complications due to the spatially complex orientation of the source and target vessels. These difficulties are mainly attributed to the two-dimensionality of conventional imaging technology (x-ray fluoroscopy) with its inadequate visualization of the complex and pronounced patient-to-patient variations in vascular configuration. Previous experiments with in situ fenestration using conventional imaging and intervention control were unsuccessful and were abandoned clinically. Based on the modules realized to date, TIPSS instruments have now also been developed to make the critical step of transhepatic puncture of a branch of the portal vein during this intervention more accurate and safer. The first prototypes are available and are also being tested in phantom and animal models.

The results of in situ fenestration of aortic prostheses have already been presented at various international conferences (including BMT 2012) and have received an Abstract Prize of the Researcher Award “Experimental Radiology 2012”.

Patim innovating medical technology in.nrw patient customized engineering in aachen

"Development and imaging of patient-optimized implants"

Currently used cardiovascular implants often show severe complications in clinical application, e.g. development of thrombi, infections or re-stenosis. Moreover, the inability of synthetic implants to grow and remodel often results in a loss of function after a few years, again necessitating surgical interventions to replace the implants.

Despite promising pre-clinical results, the translation of scientific knowledge into innovative products has been very slow in the field of tissue engineering, clearly hampering sustainable development of therapeutic concepts in the past. Therefore, there is an increased need for action, especially in non-invasive in vivo diagnosis of implanted prostheses. Little knowledge is currently available on the factors and processes affecting in vivo behavior of tissue-engineered implants and the course of tissue regeneration. The development of non-invasive imaging methods is therefore necessary to ensure detailed monitoring and documentation of the in vitro culture and in vivo performance of biological implants. The information content per experiment can be increased significantly by the availability of these imaging concepts, resulting in decreased costs and numbers of animal experiments needed in pre-clinical tests. In addition, time courses can be imaged in the same experimental animal, ensuring the comparability and standardization of the experiments.

Tissue engineering concepts are increasingly gaining importance as factors that bolster the biocompatibility and optimize the function of cardiovascular implants. Production of biological implants comprising both technical components and, for example, recipient cells, allows a specific patient-customized therapy. The Patim project is thus focussing on the development and optimization of tissue-engineered vascular prostheses and establishing non-invasive imaging techniques that permit monitoring of dynamic changes of implants in vivo.

The vascular prosthesis developed within the framework of the project consists of a textile scaffold structure covered with a cell/fibrinogen coating. The inner lumen of the graft is coated with endothelial cells for enhancing biocompatibility in the bloodstream. In this way, a natural vessel is optimally mimicked. Both the cells and the fibrinogen are obtained from the patient/experimental animal (autologously), thus significantly reducing inflammation reactions.

Within the scope of the Patim project, researchers have succeeded in visualizing the textile scaffold structures via Magnetic Resonance Imaging (MRI) by embedding a contrast agent in form of iron oxide nanoparticles into these textile structures. As a result, it is possible to monitor the exact position of the scaffold structures as well as degradation kinetics. The labelling of colonizing endothelial cells with iron oxide nanoparticles has also enabled acquiring data on in vitro cell cultivation, simultaneously opening up the possibility to follow up the cells in vivo.

In addition to labelling procedures with iron oxide nanoparticles, imaging concepts involving fluorine (19F) are also to be tested in the Patim project. By means of MRI, fluorine-containing compounds can be detected in tissue with a high specificity. Fluorine imaging can be combined with regular proton imaging of tissues in order to benefit from the excellent tissue contrast capabilities of MRI. The highly fluorinated polymeric compounds used for implant labelling can be applied by means of simple coupling chemistry to the textile surface. Micellar fluorine compounds, which can be introduced in high concentrations into the colonizing cells, are used for cell labelling with 19F.

Specific radioactively labelled PET probes have been developed to allow conclusions to be drawn about inflammatory reactions. These probes serve as inflammation markers and can be localized in vivo using modern high-resolution three-dimensional detection systems. In the last phase of the project, the information contained in the MRI-PET hybrid imaging is to be recorded and analyzed, thereby enabling a detailed characterization of tissue-engineered implants in vivo.

Guest Commentary

Dr. Cord Schloetelburg
Head of Deutsche Gesellschaft fuer Biomedizinische Technik
(DGBMT – German Association for Biomedical Engineering) within VDE

The main benefit of personalization is patient oriented: Medical treatment becomes more specific, less traumatic and safer. This is a challenge for manufacturers, since medical engineering has still to be efficient and affordable with respect to its application. Furthermore, the clinical proof of patient's benefit is a difficult issue because of the comparatively small groups of patients. It will take time to bring personalized medical devices to the market in a relevant scale and a reimbursement system is needed that rewards the respective benefit. However, Germany is in general well positioned, since "break-through-innovations" are result from close cooperation between research and business. Aachen has particular strengths in medical imaging and bio-implant technology, both closely related to personalized medical products.

Partners:

- **Experimental Molecular Imaging (ExMI), Helmholtz-Institute for Biomedical Engineering, RWTH Aachen University**
  Univ.-Prof. Dr. Fabian Kießling
  e-mail: fkiessling@ukaachen.de

- **Department for Cardiovascular Tissue Engineering, Helmholtz-Institut for Biomedical Engineering, nstitute for Textile Technology, RWTH Aachen University**
  Univ.-Prof. Dr. Stefan Jockenhövel
  e-mail: jockenhoevel@hia.rwth-aachen.de

- **Department for Experimental Medicine and Immunotherapy (AME-EMI), Helmholtz-Institut for Biomedical Engineering, RWTH Aachen University**
  Prof. Dr. Dr. Stefan Barth
  e-mail: barth@hia.rwth-aachen.de

- **Department of Surgery, University Hospital Aachen (UKA)**
  Prof. Dr. Uwe Klinge
  e-mail: uklinge@ukaachen.de

- **Institute for Molecular Cardiovascular Research (IMCAR), RWTH Aachen University**
  Dr. Heidi Noels
  e-mail: hnoels@ukaachen.de

- **Department of Nuclear Medicine, RWTH Aachen University**
  Univ.-Prof. Dr. Felix M. Mottaghy
  e-mail: fmottaghy@ukaachen.de

- **Chair for Laser Technology (LLT), RWTH Aachen University**
  Dr. Elke Bremus-Köbberling
  e-mail: elke.bremus@ilt.fraunhofer.de

- **Institut für Textiltechnik (ITA), RWTH Aachen University**
  Dipl.-Ing. Philipp Schuster
  e-mail: philipp.schuster@ita.rwth-aachen.de

- **3T TextilTechnologieTransfer GmbH**
  Dipl.-Ing. Uwe Merklein
  e-mail: info@3t-gmbh.de

- **Matricel GmbH**
  Dr. Ingo Heschel
  e-mail: heschel@matricel.de

- **Pharmed Artis GmbH**
  Dr. Georg Melmer
  e-mail: georg.melmer@pharmedartis.de

- **Philips Technologie GmbH Research Laboratories**
  Martin Weibrecht
  e-mail: martin.weibrecht@philips.com

I³-Assist

innovating medical technology in.nrw patient customized engineering in aachen

"HLM and ECLS all in one"

In surgery as well as in diseases treated without surgery, it may become necessary to support the heart and/or lung functions of a patient. This support ranges from a partial assistance of one organ to the complete takeover of the functions of both organs. For this purpose, mechanical systems outside the body (extracorporeal) are used. The tasks the body can perform no longer are provided by individual functional units of these systems. Mechanical pumps are used to support the heart whereas the lung function is replicated using membrane oxygenators.

The project I³-Assist aims at the development of a highly integrated system of modular components for such life-support units. This system can be used short-term as heart-lung machine (HLM) as well as long-term for extracorporeal life support (ECLS). Use of HLM is intraoperative, whereas ECLS is used in intensive care. The system is also interactively adjustable to meet the treatment needs of the patient by adding or removing modules.

The modular system is specifically adaptable to the requirements of the user. The high degree of modularization makes it adaptable to persons in all age and weight categories. As a result, the treatment of very young patients is facilitated as well as the adaption to the wide range of comorbidities seen in elderly patients.

The new technology will make "seamless" switchovers between HLM and ECMO possible, and vice versa. Without replacing the entire circulatory system, as currently necessary, the I³-Assist system can be adapted to the changing individual therapeutic needs of the patient. Patient traumatization and treatment costs are reduced.

The modular design also aims to reduce costs of both production and transport for the manufacturer as well as the costs of acquisition and storage for the users. This could reduce treatment costs, save resources, and simplify procedures.

The I³-Assist system has a compact design, making it readily mobile for both the internal hospital patient transport (between operating room, intensive care, and diagnostic wards) and the transfer between different hospitals (mobile intensive care unit or helicopter transfer).

As a result, a product is being developed which eliminates the existing limitations of the ECMO market by providing greater efficiency and safety as well as lower costs and less patient traumatization – and facilitating direct connections to other treatments. New therapies are revealed by these potentials that further widen the field of possible indications, thus leading to a more widespread use in clinical applications.

Partners:

- **Department of Cardiovascular Engineering, Institute of Applied Medical Engineering Helmholtz Institute of RWTH Aachen University**
  Univ.-Prof. Dr.-Ing. Ulrich Steinseifer
  e-mail: steinseifer@hia.rwth-aachen.de
  Jutta Arens
  e-mail: arens@hia.rwth-aachen.de
- **Medos Medizintechnik AG**
  Priv.-Doz. Dr. Jürgen O. Böhm
  e-mail: j.böhm@medos-ag.com
- **Surgical Intensive Care – Adults, University Hospital Aachen (UKA)**
  Dr. Rüdger Kopp
  e-mail: rkopp@ukaachen.de
- **qcmed GmbH**
  Peter Knipp
  e-mail: p.knipp@qcmed.de
- **Membrana GmbH (associated)**


RAUMEDIC-ECC-noDOP-Blood

Guest Commentary

Prof. Dr. Fridtjof Nüsslin,
Technische Universität München

For a number of years now, promotion of high-tech in the field of medicine has been at the top of the priority list in North Rhine-Westphalia. The reasons are obvious: the strength of the economy here is based on a highly developed industrial and research landscape, on the other hand medical engineering is a booming growth industry with a high degree of innovation. Of course considerable effort will be required to maintain Germany's current leading position on the world market. Particularly important, I think, is the close interaction of research and industry. Innovation in medical engineering will only succeed if the path from idea to product is kept as short as possible and remains a two-way street. This applies particularly to the current "megatrend" personalized medicine, from which a significant impact on the entire healthcare system is expected, both economically and socially. Previously, deviations from established, homogeneous clinical pictures were considered insignificant variants from the norm, but rapidly progressing biomedical research, especially as regards determination of the biological and molecular causes of disease and genetic patient mapping, are now placing the individual aspects in the foreground when selecting diagnostic and therapeutic measures. The standardized treatment regimen – "one size fits all" – is being replaced by an individually tailored approach. A higher level of efficiency, a reduction in side effects and cost savings are among the expectations. Herein lies the great potential of individualized medicine.

Biomedical research, for example genome sequencing, as well as the many physical-technological innovations in areas such as molecular imaging, are among key pioneers of individualized medicine. Patient customized engineering must be seen as a response of biomedical engineering to the call for more individualized medicine. This is especially the case for diseases characteristic of advanced age – cardiovascular conditions, cancer, diabetes and Alzheimer's disease.

The new strategic initiative PaCE "Patient Customized Engineering" from North Rhine-Westphalia must be seen in this context. Within the framework of the now somewhat dazzling concept of personalized medicine, PaCE clearly shows the way clarifies the thematic boundaries: technology tailored to the individual patient. Examples of this approach include the projects already launched in the Aachen-based cluster "medtec in.nrw" in cardiovascular medicine. One can only wish the PaCE initiative every imaginable success. PaCE will certainly encourage the founding of a number of high-powered R&D groups, bring together research and industry in the field of health research and make the fledgling field of physical-technical professions in medicine more attractive to budding scientists.

Recommended actions

Through numerous initiatives, Germany and in particular North Rhine-Westphalia has attained a pioneering role in the development of patient customized engineering. Further efforts must be made in science, economics and health policymaking, to maintain and expand on this advantage nationally and internationally: broadening of the research base, translation of the results into economically meaningful implementations in standard care contexts. Then the investment in patient customized engineering will have resulted in sustainable progress that patients will benefit from.

The priority actions necessary to achieve the above-mentioned objectives include all stations in the value-added chain of medical technology innovation, also including the users and caregivers:

- Interdisciplinary training and education for increased interdisciplinary cooperation between doctors, engineers and scientists.
- Development of suitable clinical study models and procedures for patient customized engineering based on individualized study protocols and the fundamentally changed supply paths. In addition, it is increasingly important internationally to attract clinical partners for feasibility studies and pivotal clinical trials.
- Development of benefit analyses and concepts to prove the benefit of patient customized engineering compared to the current gold standard. Last but not least, this promotes acceptance by clinicians and patients. In addition, it is necessary to promote the financing of patient customized engineering by healthcare insurers in primary care by means of healthcare economics analyses.
- Development of appropriate approval procedures for individualized medical devices, especially those in to the highest risk category.
- Need to establish and test new business models, in companies as well as across sectors by service providers so as to reflect the changing supply situation for patient customized engineering.
- Resolution of the economic dilemma between mass production and customization by promoting the development and model introduction of new production processes as part of overall care. Innovative concepts of automation and quality assurance in production are required to tap the great potential of „bioimplants“.
- Creating a legal environment for clinical and para-medical professions regarding the application of patient customized engineering with regard to security and safety for data, users and patients.
- Further development of patient adaptation by developing appropriate modelling and simulation methods, i.e. taking into account morphological characteristics by means of preoperative imaging.
- Creation of international acceptance of partnerships in science, business, and hospitals, in particular with regard to the major global markets.

It is not only the supply and production processes that must be adjusted to accommodate patient customized engineering. The approach in research and development must also be fundamentally restructured in view of rapidly increasing complexity in this field. One approach consists in the application of the methodology of „systems engineering“ to the exploration and development of innovative medical devices.

The trend of personalization ushers in a new era in medical engineering. Some research collaborations are already here and initial success stories are emerging. The important thing now is to secure the foreseeable progress and to firmly and sustainably maintain the implementation of innovative products and treatments.

Contact

Cluster Development

Catherine Jungbluth, *AGIT mbH*

Dr. Stephanie Schelder, Dr. Tobias Franken, *AKM Innovationsmanagement GmbH*

Dr. Robert Farkas, *Institute of Applied Medical Engineering (AME), RWTH Aachen University*

Dr. Carin Jansen, *LifeTecAachen-Jülich e.V.*

innovating medical technology patient customized engineering in aachen

e-mail: **kontakt@medtec-innrw.de**

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