Final Program

STW Perspectief Program

Cardiovascular risk management by advanced medical image analysis

(CARISMA)

April 2010

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Cardiovascular risk management by advanced medical image analysis

CARISMA

Contents

Summary

Advances in medical imaging devices have drastically increased the capabilities to (non-invasively) study the human body; they not only provide detailed three- or four-dimensional morphological information on anatomy, but also on function and physiology. In addition, processes can increasingly be studied at a large range of spatial and temporal scales, thanks to – amongst others – the availability of a large number of custom-made biomarkers that enable the visualization of specific processes at the cellular and molecular level. These developments have a large potential to improve the understanding of disease processes, which in turn may lead to possibilities for drug discovery and development, improved diagnosis, prevention and early detection of disease, improved treatment monitoring, and improved treatment options, e.g. replacing conventional open surgery by image-guided, minimally invasive interventions.

With these advances, the sheer size, complexity, and heterogeneity of imaging data available for biomedical research and clinical practice have increased enormously. Consequently, the lack of adequate image processing techniques to analyze these data has become a main obstacle. **There is an urgent need for solutions which enable the integrated analysis of complex, heterogeneous imaging data, which have been acquired with different imaging modalities and at different time points. This poses a formidable challenge, and requires a new generation of advanced image processing techniques, which can only be developed through an intense collaboration between the end users (clinicians), leading academic centers in the field of medical image analysis, and industry**.

The Netherlands has an excellent name worldwide in the field of medical image acquisition and analysis with applications, in e.g. cardiology, radiology, neurology and oncology. As for industry, next to Philips Healthcare and the European headquarters of major global imaging companies, there are also many SMEs with worldwide marketing positions in The Netherlands; some of these companies are spin-offs from academia. The time is ripe to join forces in a coherent activity, to integrate academic and industrial activities, and thereby achieve a breakthrough to fortify and extend the currently already strong economic position.

This program aims to develop, validate and valorize a new generation of medical image analysis methods, which would enable the integrated analysis of heterogeneous and 4-D medical imaging data to improve disease detection, diagnosis, treatment, and prognosis. The focus of the program will be on the generation of image-based technology that yields **improved management of cardiovascular disease**, an area with large societal relevance and economic potential.

Current status and (inter)national context

Position

The Netherlands has an excellent name worldwide in the field of medical image acquisition and analysis with applications in cardiology, neurology and oncology. In terms of publications in medical imaging over the past five years, The Netherlands has the 5th place by contributing 6.3% of all these publications, not corrected for the number of scientists or inhabitants. In the IEEE Transactions on Medical Imaging, The Netherlands holds 7th place in the total number of submissions and publications, after the USA, Canada, UK, Germany, France and China.
The development of competitive medical image analysis approaches requires university research groups with a long track record and a substantial infrastructure, plus dedicated imaging companies with a global track record in cardiovascular applications (Figure 1).

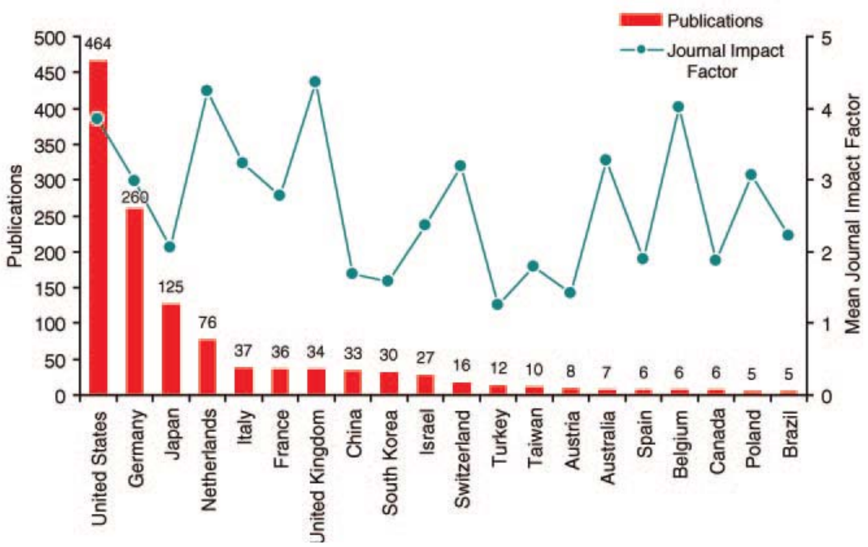

Figure 1: Publications about cardiac CT over the years 1996-2006; The Netherlands plays a dominant role and publishes in the highest ranking journals.

In 2007 the medical imaging groups in The Netherlands have decided to further synchronize their activities by setting up The Netherlands Forum for Biomedical Imaging (NFBI; www.nfbi.nl). NFBI hosts biannual meetings which bring together leading scientists, PhD students, clinicians, and industrial developers in biomedical imaging. The last meeting on September 10, 2009 was visited by approximately 100 persons from academia and industry, which underlines the size of the national academic and industrial research activities in this field. The mission of NFBI is to provide a platform for exchange of scientific research in biomedical imaging, in particular biomedical image analysis, and to foster collaboration between academic groups, ànd between academia and industry. The platform aims to manifest itself as a representative of Dutch biomedical image analysis research and development at the national, European and international level.
The great advantage of The Netherlands is its top infrastructure of university medical centers, world-class imaging groups both in these UMCs and at the Universities of Technology, global Clinical Research Organizations, and dedicated and internationally recognized imaging companies, all at short travel distances. This supports greatly the current national developments towards more focus and mass in research, clinical usage and subsequent valorization by the companies. Consortia such as the Medical Delta (Erasmus MC, TU Delft and LUMC) and proposals of Centers of Research Excellence (CoREs) within the NWO Theme New Instruments in Health Care (NIG) are a result of that. The participating companies already have licensing agreements with the major OEM and PACS companies worldwide.
The European Association of Radiology founded in 2006 the European Institute for Biomedical

Imaging Research (EIBIR); Prof. Krestin (Erasmus MC Rotterdam) is the chair of EIBIR. In EIBIR more than 200 European science laboratories and clinical departments participate. One of the four research pillars in EIBIR is biomedical image analysis, which underscores the great importance of biomedical image analysis research in Europe; this effort is led from The Netherlands. Likewise, the European Society of Cardiology representing more than 50,000 cardiology professionals has as its mission: “to reduce the burden of cardiovascular disease in Europe”, whereby imaging plays a dominant role in the many working groups. In the USA the National Institute of Biomedical Imaging and Bioengineering (NIBIB) was established in 2000 to support fundamental research in bioengineering and bioimaging science and transferring the results to medical applications; their yearly budget is 300 M$.
The following quote on the website of the European Science Foundation (ESF) very much supports the CARISMA intentions: “Medical imaging is currently one of the most important areas in biomedical research: in basic research in biosciences and medicine, in translational research – bringing the results from the laboratory to the bedside – and in clinical research, including pre-clinical research, as well as the development of new advanced diagnostic methods for research and better patient care.”

The need for this Program

The earlier IOP Beeldverwerking program with 46 projects (1996-2007) has contributed significantly in stimulating the collaboration and valorization between the university imaging groups and the imaging industry. However, since that time a major imaging program has not been created, making this new program very necessary.
This Perspective program is also fully in line with NWO’s Nieuwe Instrumenten in de Gezondheidszorg (NIG), an initiative supported by STW, ZonMW, FOM, ICTRegie, the Ministry of Health, Welfare and Sport (VWS), and NWO. NIG wants to create a momentum for the years 2011 and following, and this STW Perspective Program would fit perfectly as a “start-up” activity in the cluster “Image Processing”. The imaging groups participated actively in the first round of grant applications of NIG in 2009 with a total of approximately 60 NIG-submissions to STW, indicating how active and alive this field is. Since that time they have organized themselves further in an attempt towards more focus and mass and have submitted proposals for the CoRE’s (Centers of Research Excellence), which currently are being reviewed.
The present program will maintain and possibly further strengthen the leading position of Dutch academic groups in image processing. In addition it will strengthen the collaboration between academia and industry, and allow Dutch industry to maintain its leading position; with both a major industrial leader (Philips Health Care) and a large number of SMEs, there is large economic activity within this field in The Netherlands. It is time to further integrate academic and industrial activities, achieving both scientific breakthroughs and fortification and extension of the already strong economic position of Dutch medical imaging industry, in particular in the dynamic field of cardiovascular imaging. While all these activities are directed towards gaining momentum in financial support, CARISMA should function as a booster to energize future opportunities.

Complementarity

The program is complementary to imaging efforts subsidized by or submitted to other large funding programs such as TIP, CTMM, BMM, TeRM. In these programs, image analysis – if present – plays a supporting role to serve the primarily biomedical research questions; innovation in image analysis methodology and software is outside the scope of these programs. The current program is in line with the theme’s of VNO/NCW, the priorities of the Ministry of Economic Affairs, the key areas High-tech Systems and Materials of the Innovation Platform, the reports of the COS (Commissie Overleg Sectorraden), and the NWO Strategy 2007-2010: Science Appreciated. The subject of the proposal is also in line with the WHO’s priority ‘Medical Devices’. The WHO report underscores the importance of research on and development of medical devices, including medical imaging, and the need for further support by the governments and other stakeholders.

The challenges

Recent developments in medical imaging technology enable detailed assessment of human anatomy, physiology and pathophysiology at different spatial and temporal scales. As a result, the role of medical imaging in disease detection, treatment and prognosis is rapidly increasing. However, the sheer magnitude and complexity of imaging data poses a new challenge, which is increasingly recognized as a main obstacle for progress in this field. By combining the multidisciplinary expertise from academia and industry, and building on the excellent medical imaging infrastructure in The Netherlands, this program will take up the challenge to fully exploit all the information available in multi-modal cardiovascular imaging data, for improved diagnosis, prognosis and treatment of cardiovascular disease. In The Netherlands over 43,000 out of 136,000 deaths are caused by cardiovascular disease in 2005 (source CBS). In a large number of cases, there are no signs of coronary heart disease prior to the coronary heart event, thus often resulting in irreversible damage or death prior to any medical intervention. Accordingly, early detection of coronary heart disease (CHD) remains of paramount importance as well as the subsequent medical or surgical treatment and follow-up.

The scientific challenges in this program lie in:
- (i) the development of innovative algorithms that enable integrated analysis of cardiovascular imaging data acquired with a large variety of acquisition techniques;
- (ii) to implement these technologies for improved cardiovascular disease detection, diagnosis, treatment and prognosis.

Owing to the different characteristics of imaging techniques, the large variability in patient anatomy, pathology and (patho)physiology, and the occurrence of both cardiac and breathing motion, these challenges require a multitude of scientific advances, including:

1. **Information Integration:** Development of methods that integrate multi-modal, heterogeneous cardiovascular imaging data. Challenges include integration of anatomical and functional data, integration of imaging data of the vascular system with images of the heart, and integration of imaging data at different scale levels (including molecular imaging data).
2. **3D & 4D cardiovascular image analysis:** Development of methods that enable automated quantitative image analysis and segmentation of spatiotemporal (4D) cardiovascular imaging data. Challenges include automated analysis of the heart anatomy and function over the entire cardiac cycle, and automated segmentation of the vessel lumen and vessel wall of the entire cardiovascular system.
3. **New prognostic indicators:** Development and validation of prognostic imaging biomarkers for cardiovascular disease from large patient and population studies. Challenges include the identification of image features as prognostic biomarkers, and the integrated analysis of these features in combination with other risk factors in a large number of epidemiological and patient studies which are carried out by the different University Medical Centers participating in the project.
4. **Improved guidance in image guided interventions:** Computer-aided navigation and motion correction to support cardiovascular interventions. The main challenge is to correct in real time for cardiac and breathing motion so as to provide actual and detailed 3D information to the cardiologist/radiologist during the intervention.

Program scope

Based on discussions in the Workshop held on January 29, 2010 at NWO in The Hague, the scope of this Program from an application point of view is as follows:

The program, through its projects, should focus on the development and validation of advanced cardiovascular image analysis methods, for improving cardiovascular disease detection, diagnosis, treatment, prognosis and follow-up. Consequently, the program primarily considers the heart and/or the vascular system in relation to other organs. Accordingly, topics like quantitative image analysis in stroke and lung perfusion are within the scope of the program, whereas e.g. tumor vascularization and tumor perfusion are explicitly outside the scope. The program is specifically aimed at image analysis (“images in, numbers out”); however, joint optimization of image acquisition and subsequent quantitative analysis will be considered if the focus is on the latter. Also, image fusion and visualization to support quantitative image analysis or image guided interventions is considered to be within the program scope. Clinical validation of developed methods on large datasets is definitely within the scope of the program.

From a more technical and scientific point of view, the focus must be directed to one of the 4 challenges mentioned above, and which are repeated here:

1. **Information Integration:** Development of methods that integrate multi-modal, heterogeneous cardiovascular imaging data.
2. **3D & 4D cardiovascular image analysis:** Development of methods that enable automated quantitative image analysis and segmentation of spatiotemporal (4D) cardiovascular imaging data.
3. **New prognostic indicators:** Development and validation of prognostic imaging biomarkers for cardiovascular disease from large patient and population studies.
4. **Improved guidance in image guided interventions:** Computer-aided navigation and motion correction to support cardiovascular interventions.

Research Themes

This program will address four important technological gaps:

Theme 1: Information integration

The rapid and recent developments on the acquisition side have enabled imaging of major parts of the cardiovascular system in one examination, and a combined imaging of different functional processes. Past efforts towards automated analysis of cardiovascular images mainly focused on single imaging modalities of individual anatomical structures. These existing methods do not exploit the recently gained information richness in the novel cardiovascular imaging protocols, leaving much of the novel diagnostic potential unused. This program will fill this technological gap by developing innovative image analysis approaches that integrate information from different imaging techniques, so as to connect information on the anatomy of the heart and major vessels (the aorta, carotid arteries and peripheral arteries) with information about different functional processes as, *e.g.*, cardiac perfusion, inflammation, plaque composition and cardiac function. (Figure 2).

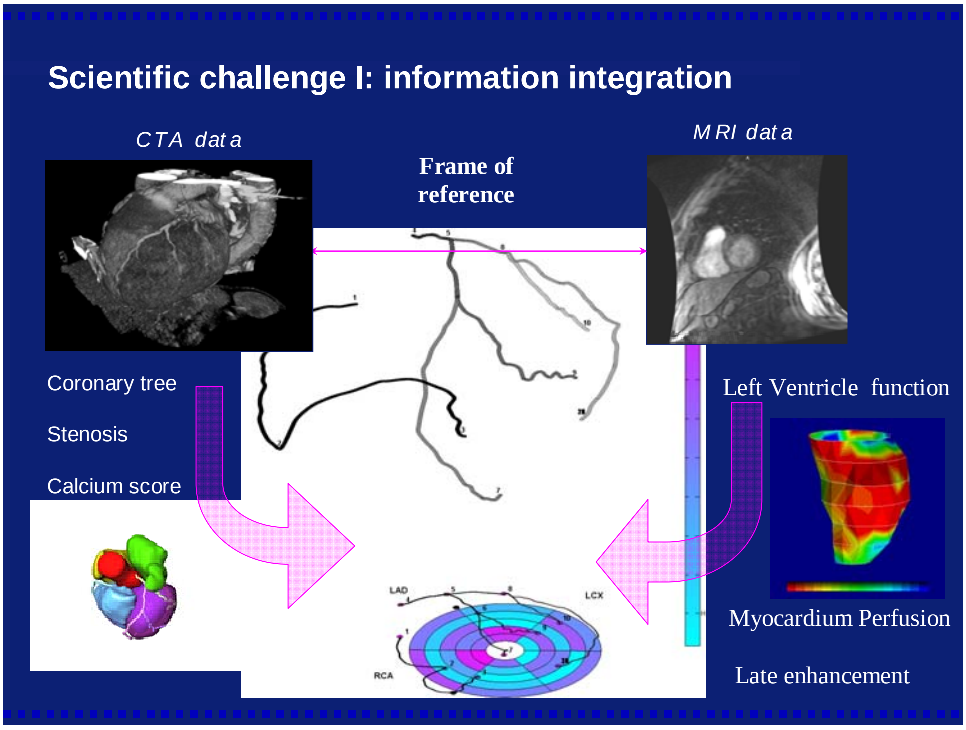

Figure 2. Integration of quantitative data from different imaging modalities will be combined to come to a complete patient-specific picture of the disease state of the individual patient. In this example, the coronary vessels from MSCT, the narrowings in the vessels and calcium from MSCT as well, left ventricular function and late enhancement (infarct imaging) from different MRI sequences, and myocardial perfusion from either MRI or nuclear cardiology. All of these data sets with widely varying resolution scales need to be registered into a common reference frame.

Theme 2: 3D & 4D cardiovascular image analysis

Since the heart is a dynamic organ, robust and accurate segmentation techniques are required to analyze the entire volumetric organ over the complete cardiac cycle. This has been demonstrated to be much harder than anticipated and available approaches have not resulted in routinely acceptable performances. New, innovative approaches are necessary to come up with solutions that will be acceptable in terms of accuracy, robustness and speed in daily clinical routine. In addition, there is an increased need for instantaneous translation of image data to functional parameters, as e.g. transvalvular flow assessment (See Figure 3).
Finally, new approaches for whole body imaging and concurrent analysis of the entire vascular system are needed, so that early signs of atherosclerotic disease can be detected.

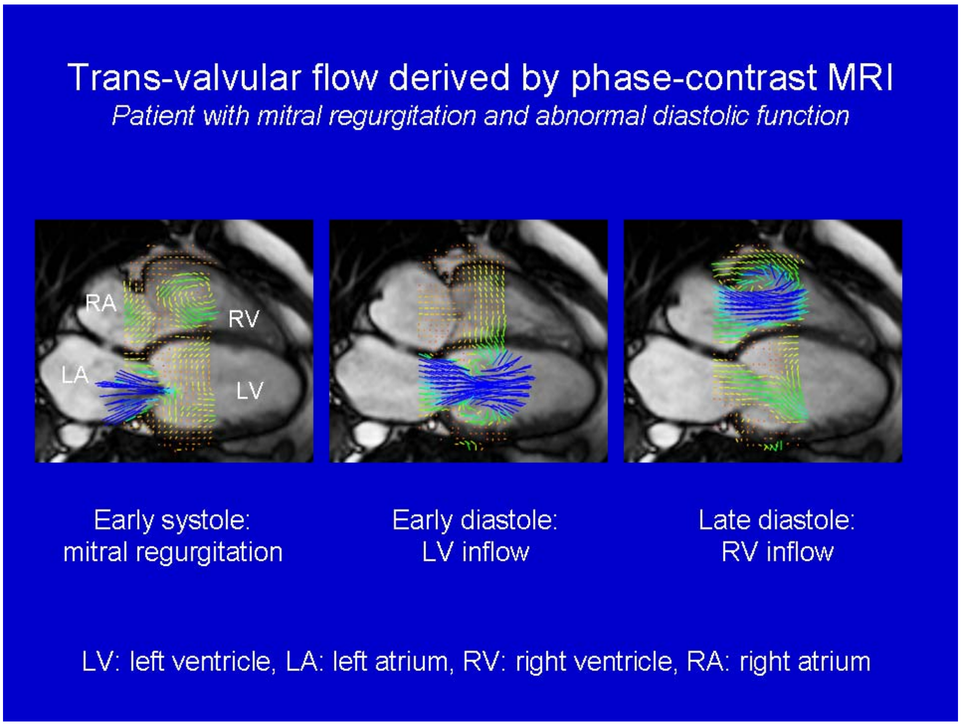

Figure 3: Trans-valvular flow assessment using 3D phase-contrast MRI with velocity-encoding in three directions. Vectors indicate magnitude and direction of blood flow throughout the cardiac cycle. Using retrospective valve tracking, trans-valvular flow across the valves can be derived to quantify the severity of mitral regurgitation and to assess diastolic function parameters.

Theme 3: New prognostic indicators

The newly established imaging options make it possible to follow large populations of patients over a prolonged period of time. By correlating image-derived measures to clinical events in this population, novel, imaging based prognostic indicators can be derived. In combination with more traditional risk factors (such as biochemical indicators), such indicators can be used for: 1) personalized early diagnosis, and 2) better prognostic estimates for improved patient management. The development of methods to derive these indicators is a new field of research. (Figure 4).

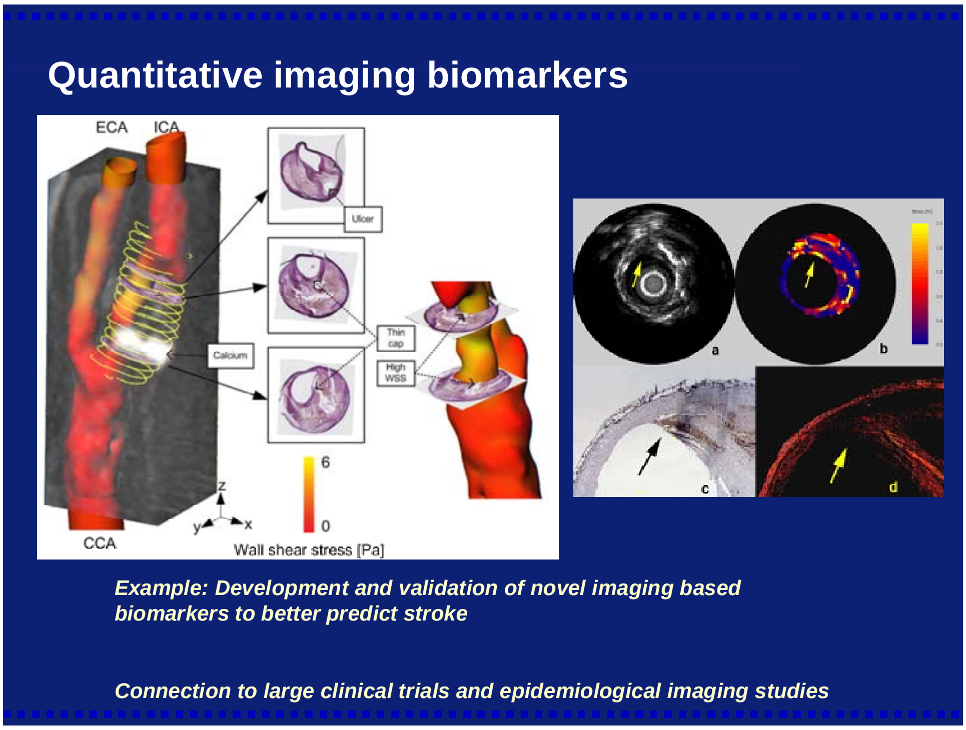

Figure 4: Imaging biomarkers which reflect the presence and state of carotid or coronary artery disease can be obtained with different imaging techniques, such as MRI, CT, and ultrasound. These imaging biomarkers may be indicative of rupture risk, and hence predictors of clinical events such as e.g. stroke.

Theme 4: Improved guidance in image guided interventions

Many types of cardiovascular interventions are currently performed under image guidance, for instance stent placement and cardiac ablation therapy. The success of such procedures heavily relies on the precise localization of the catheter position with respect to the treated site, which often is heavily moving and deforming due to breathing and heart contraction. Improved image guidance through computer aided navigation supported by motion correction algorithms would therefore greatly improve the efficacy of cardiovascular interventions. This is a novel and challenging field of research. (Figure 5).

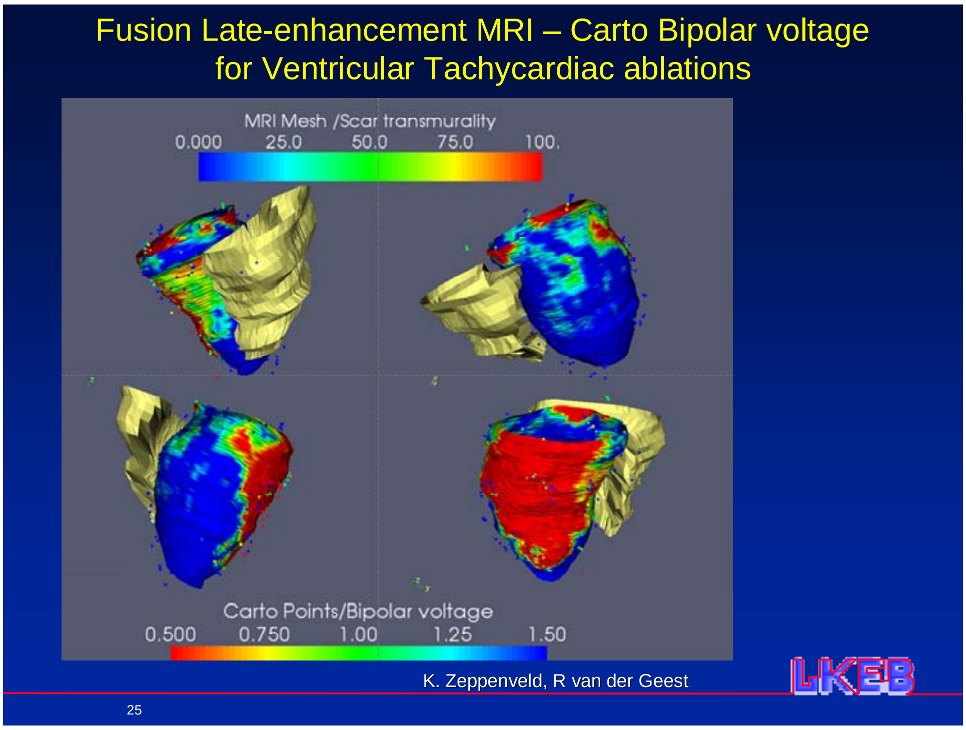

Figure 5. Fusion of late enhancement MRI with the Carto bipolar voltage approach provides essential information for the interventional cardiologist about the positions in the myocardial wall or outflow tract where ablations should take place. This diminishes the procedure time and X-ray radiation significantly, while improving the success rate of the procedure. Preferably this should be done on-line and in real-time in the catheterization laboratory, requiring compensation for breathing, etc.

Valorization

The results of the projects should be advanced medical image processing techniques, enabling the integrated (quantitative) analysis and visualization of multi-modal medical imaging data, which should have been validated by medical experts for specific clinical applications. The developed image analysis technology should be transferred or be transferable to the interested imaging companies, leading to fast time-to-market (1-2 years) development of their product portfolios and worldwide commercialization.
Alternatively, projects can aim at novel Computer-Aided Diagnosis (CAD) and prognostic approaches validated with the clinical partners , resulting in licensing contracts with the same imaging companies. The involvement of clinical experts in all the phases of development and validation of the technology maximizes the chances of market acceptance. The results may also lead to new start-ups.
The availability of these new image analysis techniques should have impact on the daily routine of clinical diagnostics and treatment. First, it enables the medical specialists to deal effectively with the different anatomical and functional data from multiple information sources. Second, the developed image analysis techniques provide a solid quantitative basis for improved clinical diagnostics as well as clinical research in the hospitals. This leads to a more evidence-based approach for diagnosis, therapy planning, and therapy monitoring, and thus better, patient-individualized, treatment. Third, it is expected that developed techniques will play a crucial role in effectively carrying out large screening studies. Because of the targeted high accuracy and reproducibility, the size of patients groups to test a certain hypothesis in a clinical trial can be reduced, facilitating faster and cheaper drug discovery and development; this will be of great and immediate interest to Clinical Research Organizations (CROs) and pharmaceutical companies.
The market potential for advanced image analysis is enormous and on a worldwide scale: the daily interpretation of all medical data sets takes place behind workstations with advanced imaging software all connected to radiological picture archive and communication systems (PACS). This means that every hospital, research group, or pharmaceutical company will have multiple to dozens of concurrent floating licences of such software packages.
The CARISMA program intends to provide the tools for many of these applications. It is the expectation that within ten years almost all clinical imaging datasets will be diagnosed with computer assistance. This program will provide an essential stimulus to bring The Netherlands to the top worldwide in this competitive field.

Application perspective

Utilization is a priority issue throughout the execution of the program. Workshops, in which the output of the program will be discussed, will be organized twice a year; integration of the results and the existing expertise will be important subjects in these discussions. Experience from other programs has proven that in addition to user group meetings in individual projects, workshops with interdisciplinary contacts strengthen the overall effectiveness. The added value of such workshops within programs is clearly demonstrated by the fact that the field usually remains organized in such a collaborative sense after the end of the program (see the enduring effects of the IOP Beeldverwerking). This strategy will, furthermore, likely lead to new high-tech starters, which will generate employment for ICT professionals. In addition, the CARISMA program will provide a strong basis for Dutch participation in international medical image initiatives.
The program will have also benefits for HBO education in The Netherlands, by providing internships for HBO-students, stimulating their participation in workshops, and creating positions on a technical expert level after their graduation.
Partners in this program should have experience in the transfer of knowledge and/or software modules/libraries from university research groups to industry, either (major) OEM partners or SMEs. Successful execution of the proposed research program should lay a firm fundament for long-term collaborations between academic centers and industry. SMEs in turn will be able to

license their new software products to their global partners, thereby reaching the entire world.

Duration and budget

A program duration of 6 years is scheduled, with a total budget of 6.0 M€. It is estimated that the program execution will involve 12 PhD students for periods of 4 years, 5 post-docs for periods of 4 years, 5 physician-scientists for periods of 4 years, 400k€ for material expenses, including manufacturing or procurement of phantoms and travel expenses, totaling 4.5 M€; the remaining 1.5 M€ constitute the industrial commitments.

For the 12 semi-annual program level workshops a total budget of k€ 70 has been reserved.

Organisation

Proposals and selection

The selection of proposals will be made in two steps: a call for pre-proposals and a subsequent invitation of selected applicants of pre-proposals to submit full proposals. The pre-proposals will be evaluated by the Program Committee. The STW Board will decide on the funding of the full proposals.

Program Committee

The Program Committee consists of the following experts:

Prof. dr. ir. J.H.C. Reiber, Leiden University Medical Center
Prof. dr. ir. M.A. Viergever, University Medical Center Utrecht
Prof. dr. W.J. Niessen, Erasmus Medical Center Rotterdam
Prof. W.P.Th.M. Mali, University Medical Center Utrecht, chairman of the clinical users group
Dr. ir. B. Goedhart, Medis Medical Imaging Systems B.V., Leiden
Dr. ir. R.J. ‘t Hoen, OlDelft B.V., Delft

The Program Committee will use the following considerations to evaluate if the project proposals fit the framework of the program:

- The goals of the project should fit the Program Scope;
- The project should address one or more of the Research Themes;
- The project should have a sufficiently high level of innovativity;
- The expected project results should meet a long term industrial need;
- The project should strengthen the expertise in The Netherlands in general and of the participants in the project in particular;
- The project should be multidisciplinary in the sense of collaboration between universities, clinics and companies;
- The project should not overlap with other projects in the program;
- The projects should, collectively, involve most of the cardio / imaging knowledge available in The Netherlands.

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