Cvent

Risk assessment of plaque rupture and future cardiovascular events (CVENT) by multi-spectral photoacoustic imaging

www.CVENT-2020.eu

Executive deliverable summaries

public series

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 731771, Photonics Public Private Partnership, and is supported by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 16.0160.

Project

Introduction

Due to the ageing population the request for a change in healthcare delivery becomes inevitable. As people live longer the number of hospitalizations and clinical interventions rises. This upcoming increasing necessity for medical care is underlining the need for a cost effective change in healthcare delivery. Key items in this process of change are early disease detection, improved diagnostics and advanced therapy monitoring all by means of point-of-care functional imaging.

Within this context, the focus of CVENT the consortium is on the translation of photoacoustic imaging (PAI) from a research-based image modality to a low-cost portable multi wavelength combined PAI system for vulnerable plaque imaging. Cardiovascular disease (CVD), more specifically, vulnerable plaque rupture, remains the major cause of death for people at middle age. In the carotid arteries feeding the brain, vulnerable plaque rupture initiates cerebrovascular ischemic attacks. Consequently, there is a worldwide unmet and urgent clinical need for functional information to enable in-depth diagnosis of carotid plaque vulnerability, avoiding cardiovascular events (CVENT).

The CVENT project addresses this unmet clinical need for a diagnostic method to identify vulnerable carotid plaques. Vulnerable atherosclerotic carotid plaques, an age and lifestyle related vascular disease, remain a major cause of death for men and women at middle age and is also a hallmark of generalized CVD involving other critical vascular regions like the coronary arteries. Every patient exhibiting symptoms of partial occlusion of the carotid arteries is examined with US because a matured carotid plaque is potentially vulnerable to rupture. When that happens, the content of the lesion entering the blood stream can cause stroke. In the EU this affects over 1 million people annually. According to the guidelines, the patient is operated on, if a 70-99% occlusion of the artery is found. However, only one out of nine operations is effective (Barnett 1998; Rothwell 2003). Even worse, 19 operations need to be done to prevent a single stroke. Hence, the current method to assess plaque vulnerability is insufficient.

FACTS

Call: H2020-ICT-2016-1: Photonics KET 2016

Duration: 42 months

Starting date: Nov 2016

Type: RIA – Research and Innovation Actions

Vision: Revolutionary diagnostic method to identify vulnerable carotid plaques

CVENT public project summary

Consortium

Project partners

Partner	Main role in CVENT
Esaote Europe B.V. Maastricht, NL	Medical Applications
Eindhoven University of Technology Eindhoven, NL	Functional Imaging
University of Twente Enschede, NL	Photoacoustic Imaging
Paris Descartes University Paris, FR	Cardiovascular Diseases
University of Bern Bern. CH	Light Propagation
Ruhr-Universität Bochum Bochum, DE	Reconstruction Algorithms
BrightLoop Paris, FR	Laser Diode Driver
SILIOS Technologies Peynier, FR	Optics
LUMIBIRD Paris, FR	Laser Diodes
tp21 GmbH Berlin, DE	Project Management

FACTS

10 partners from three EU Member States and one associated country (Switzerland)

5 academic partners

5 industrial partners

Partners‘ main role in CVENT indicated

Public series

Collection of summaries

What are deliverables?
Deliverables in H2020 projects are distinct, tangible or intangible outcome by the consortium members in alignment with the project objectives. Deliverables are measurable results of a project process and could be a report, a document, a website, a prototype or any other building block of an overall project. Deliverables will be published directly after the related work has been completed.

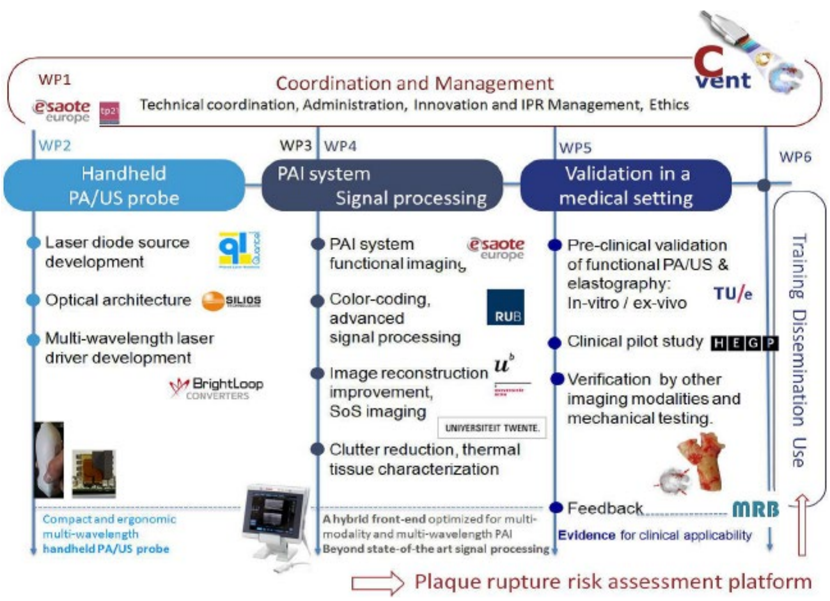
What is the CVENT goal?
The CVENT consortium wants to make photoacoustic imaging and the principal advantages over other techniques understandable, not only to clinicians, but also to the public. CVENT technology is developed in accordance to the medical needs and will lead to a commercial product ready for clinical practice.

Why work packages?
In the CVENT consortium the partners are working on different scientific and technological challenges by means of specific knowledge, structured in work packages‘. The work packages main objectives are probe development, system integration, signal processing, and validation in clinical settings (figure 1).

Our publication plan:
The CVENT consortium intends to publish short summaries of each technical work package deliverable. As a result the public will be able to follow the project progress. The CVENT consortium defined 17 technical deliverables.

The CVENT website:
Please visit www.cvent-2020.eu for further information on dissemination activities, publications and all public deliverable summaries.

The technical deliverables are:
- Architecture of PA/US probe
- First PA/US probe
- Plaque testing setup and first in-vitro results
- System architecture
- Second PA/US probe
- Promotion video
- Low level programming
- Dissemination & Exploitation plan
- Exploitation report and IRP plan
- HPC framework
- Clutter and noise algorithms
- In-vivo pilot study finalised
- PA/US probe ergonomics
- Internal workshops
- SoS implementation
- Final PA/US probe
- Tissue characterisation
- PAI-US elastography
- Image aberration correction
- In-vivo and in-vitro study



Overview of the CVENT R&D executed in six work packages

FACTS

Collection:
Summaries of 17 technical deliverables

Concept:
1 page per summary understandable by the general public

Publication:
www.cvent-20202.eu

Published by the CVENT consortium.

Summary

Deliverable 2.1
Architecture of PA/US probe

The objective of the CVENT program is to provide photoacoustic imaging (PAI) of hemorrhages into carotid lipid plaques to assess their vulnerability. That requires imaging at a high depth, which is a significant step forward for diode-based PAI.
In order to have such a system of diodes, the main idea is about determining the optimal wavelengths targeting hemoglobin and lipids, and the number of wavelengths that should be integrated into the PhotoAcoustic (PA) / Ultra Sound (US) probe while providing a good contrast, a high penetration depth, a high compactness and a low cost.
The number of wavelengths was limited to three (760 nm / 808 nm /940 nm) in order to achieve a high level of compactness and to maintain a reasonable cost for the laser diode source.

Driver :
The strategy to achieve high depth for photoacoustic imaging is to increase the laser diode peak power, meaning that the peak current delivered to the diodes should significantly be increased. Further increase in the peak current will require a higher electrical input energy which will be supported by high capacitor voltage. All this will be supported while maintaining short pulse duration. Quantel, in collaboration with Brightloop, has been worked on delivery of new "very compacted" driver (for single-wavelength laser diode) with peak current of 1500 A, which generates 2 mJ output energy in 50 ns of pulse duration.
The beam shaping system contains:
- A diffractive optical element (DOE) and focusing cylindrical lenses for homogenization,
- A prism to deflect the beam towards the focusing point

Laser diode architecture:
It is important to know that the optical performances (peak power and pulse width) strongly depend on the self-inductance, and the laser diode architecture and its connections to the driver board are the keys of optimization of this self-inductance. So, the design of connections in the multi-wavelength architecture is optimized by using two driver boards: each laser diode will be connected to its own current generator. That will also minimize the width of the laser source module, which is a strong constraint to design ergonomic probe housing.

Each laser diode source (stack) will include 10 semiconductor bars in order to obtain the required energy. With this configuration, the target performances for pulses of about 50 ns is providing (after the optical system) more than : 2 mJ at 808 or 940 nm wavelengths & 0,65 mJ at 760 nm wavelength.

CVENT PA/US laser diode probe

FACTS

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Consolidation:
Peter Brands (ESAOTE)

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October 2018

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PHOTONICS21

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Deliverable 2.2

First PA/US probe

As it has been discussed at the beginning of the research, on optimal wavelengths and laser pulse specifications, it was agreed to introduce 760 nm & 808 nm wavelengths in deliverable D2.2 to assess performances through experimental results both on semiconductor chips and on PAI at this step.

Partner (SILIOS) provided technical assistance in the choice of DOE to get the best performances at both 808 and 760 nm (as described in D2.1); and our other partner (BRIGHTLOOP) provided guidance to adjust electrical circuits of pulse generators used with 760-808 nm diodes.

QUANTEL manufactured diodes at these wavelengths including optical beam optimization in the fast axis, assembled the laser modules and performed experimental measurements for diode characterisations. Then, ESAOTE sealed PA/US probes before shipment to academic partners.

At the end of the lead time for D2.2, two prototypes, which fulfil specifications at 808 nm and 760 nm have been delivered to ESAOTE.

As it was decided to use the wavelength “760 nm” in these prototypes, output energy per wavelength was reviewed to be higher than 1 mJ (instead of 2 mJ per wavelength). The reason for that is the necessity to implement 3 diodes at 760 nm to get the same output energy than a diode at 808 nm.

As it was expected by Quantel, semiconductor bars at 760 nm provided reasonable performances, and slope efficiency was three times lower than the one of triple-junction bars at 808 nm. That is related to the series resistor of the junction at 760 nm (it is higher than the one of a single junction in multiple-junction bars) which tends to reduce the bar efficiency. Damage threshold has not been reached under pulsed operation, but driver efficiency for 760 nm wavelength turned to be poor. Further analysis will be performed by BRIGHTLOOP and conclusions will be taken into account for further driver design.

These prototypes were controlled and sealed by ESAOTE, and academic partners (TU/e and RUB) have received them in order to perform PAI to compare both wavelengths. Wavelength “760 nm” undoubtedly presents the advantage to be absorbed selectively by reduced haemoglobin. Reliability and performances of semiconductor bars at this wavelength will continue to be studied by QUANTEL.

However, the overall efficiency associated to 760 nm wavelength can become an obstacle by taking into account size and cost constraints.

CVENT PA/US laser diode probe

FACTS

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Consolidation:
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Summary

Deliverable 2.3
Second PA/US probe

The CVENT partners agreed to introduce the wavelength “760 nm” in combination with “940nm” or “808nm” into deliverable D2.3. Two wavelengths among 760; 808 and 940 nm will be integrated into these second PA/US probes. Nine non-contractual prototypes will be delivered to ESAOTE who will complete the assembly and deliver them to academic partners.

New mechanical, electrical and optical parts have been designed by working with BRIGHTLOOP, ESAOTE and SILIOS. These parts were used to provide the second PA/US prototypes; which fit for the CVENT manufacturing schedule.

SILIOS designed new DOEs to get homogenous beam in the vertical axis at 760; 808 and 940nm; and all the optical system (lenses & prism) for beam homogenization in the horizontal axis. One DOE per wavelength will be manufactured. A new etching pattern for DOE at 760 nm has been designed due to the reduced number of junctions into diode bars at this wavelength.

BRIGHTLOOP designed and provided electrical driver which generates ultra-short current pulses to operate QUANTEL’s diodes.

QUANTEL designed and manufactured diodes collimated in fast axis, with wavelengths and integrated them with SILIOS’s optical system and BRIGHTLOOP’s electronic driver. All these parts were assembled in the laser diode source by QUANTEL. Experimental measurements for laser diode source characterisation were performed by QUANTEL.

Pulse characteristics of diodes at 760 nm & 940 nm were good (pulse width, energy) thanks to adjustments in the electrical circuits. The driver efficiency for these wavelengths turned to be very well designed.
Prototypes are delivered to ESAOTE and academic partners to perform PAI to obtain first images and results.

QUANTEL will continue to evaluate laser source performances and further analysis with CVENT partners will confirm the design to the final prototype D.2.4.

The mechanical design will be slightly reviewed for the final prototype D2.4

CVENT PA/US laser diode probe

FACTS

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Summary

Deliverable 2.4
Final PA/US probe

The development of the final laser module prototype is part of work package 2 (WP2) that describes research and development tasks, which need to be achieved, to provide to the consortium the most compact multi-wavelength laser diode source. This prototype should still within specification in terms of output energy, beam shaping, duty cycle and efficiency.

Initial specifications of such a laser source were defined during task 2.1 and reported in deliverables D2.1 entitled "Architecture and specifications".
In close cooperation with UTWENTE, UBERN and RUB that provided simulations and feedback on photoacoustic imaging with the various PA/US prototypes (D2.2 & D2.3), LUMIBIRD has taken care that initial specifications were still valid throughout the program.

CVENT PA/US laser diode probe

Hence, after all feedbacks, based on simulations and tests, from CVENT partners, revised specifications were discussed and all partners then agreed to implement one wavelength and trying to increase output energy by integrating capacitors with higher value on the driver of the final probe. Then, this agreement became the reference for designing the final one-wavelength laser module prototype.

Packaging of the laser diode (LD) is led by LUMIBIRD, and mechanical integration of laser source is led by ESAOTE. The design and experimental characterisation of the final prototype which is produced at LUMIBIRD, and sent to ESAOTE for integration of the ultrasound transducer and sealing, and then distributed to academic partners for evaluation of photoacoustic imaging performances.

Finally, D2.4 prototypes will contain two stacks, new drivers (with new capacitors), and a new optical system. The major improvement in the ergonomic of the probe (strong reduction of the rear volume) was achieve by tilting the source and the optical system. This was made possible by a strong cooperation in between ESAOTE, LUMIBIRD and SILIOS for the design of the new optical system and its mechanical integration.

Experimental measurements for laser diode source characterisation were performed by LUMIBIRD, and three non-contractual prototypes, of this final design D2.4, are delivered to ESAOTE according to the deliveries planning.

In April 2019, WP2 is on track with respect to the project schedule and technical specifications linked to the delivery of the final wavelength laser module prototype has therefore been successfully completed.

FACTS

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Summary

Deliverable 3.1
Ultrasound Photoacoustic System Architecture

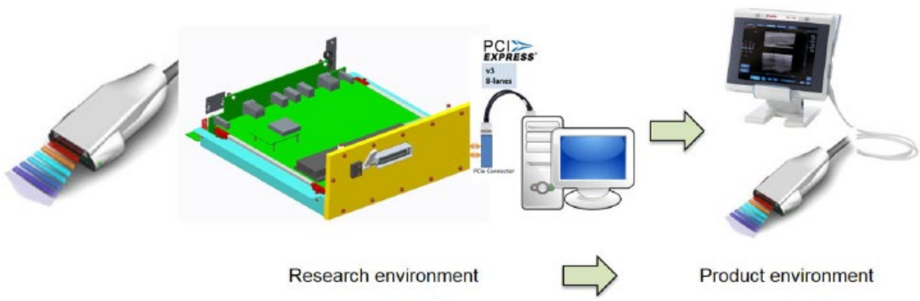
Deliverable D3.1 describes the architecture and the specifications of the CVENT photoacoustic ultrasound (PA/US) platform to be used for characterisation, diagnosis and monitoring of carotid plaque vulnerability.

Ultrasound is promising for point-of-care imaging because of its real-time display, high temporal and spatial resolution, low cost and safe of use. However, it falls short in terms of functional imaging. On the other hand optical techniques provide high contrast by the pronounced optical absorption variations in tissue and functional imaging when probing spectral features, but optical scattering limits the resolution of purely optical methods. The combination of both imaging modalities (ultrasound and light) will provide the depth and resolution of ultrasound and absorption contrast and functional imaging of multi-wavelength light.

Functional imaging, the extraction of information regarding physical or chemical processes in tissue and their alteration through disease, is a crucial element for early disease detection and treatment monitoring. Therefore, the development of an US device that allows imaging of structure and function is essential. For this reason, the objective of CVENT is on functional "photoacoustic imaging" (PAI). This will result in a fully integrated multimodal PAI system optimised for screening, in-depth diagnosis and treatment monitoring of carotid plaque vulnerability. The measurements will be focused on plaque composition and structure, size and shape, as well as mechanical properties.

The **CVENT PA/US system** will be developed in different phases. In the first phase it will serve as a dedicated open research platform with a direct high bandwidth connection of the raw ultrasound signals (RF-data per element) to an external PC.

During the CVENT project this ultrasound research platform (available for the CVENT partners) will serve as a R&D platform for research on functional PAI and advanced ultrasound beam forming. In the product development phase the CVENT proven R&D platform will be integrated in a next generation US platform ready for PAI.



The research platform with a direct high bandwidth connection of the raw ultrasound signals (RF-data per element) to an external PC will serve as an open low level controllable research and product development platform.

FACTS

Author:
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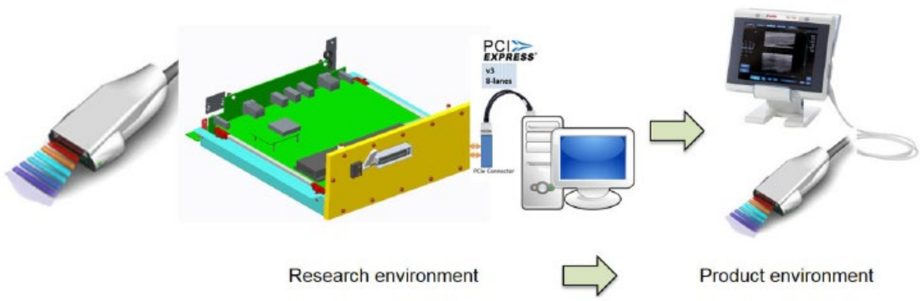
Summary

Deliverable 3.2
Low level control of the CVENT Research Platform

Deliverable D3.2 describes and shows the **low level software control manual** of the CVENT photoacoustic/ultrasound (PA/US) research platform . This CVENT research platform is used by the different partners for testing, verification, validation and small clinical studies. It is an open research platform where the research teams can control by themselfes:
1) US and laser transmission,
2) US and PA data acquisition,
3) the data link between the acquisition platform and the external PC and
4) the data storage or data processing of the acquired US/PA data.
All the groups working with the CVENT photoacoustic research platform will get a manual and in depth course on how to use the low level control of the CVENT research platform via workshops at ESAOTE. The research platform and low level control will be modified during the project based on feedback from the different CVENT partners. This process of improvements will continually be driven by the ongoing developments on the CVENT PA/US probe prototypes, ongoing experiments and the small clinical studies.

The CVENT research platform will also be important for the off-line and real-time implementation and testing of "Photoacoustic imaging" (PAI) signal processing algorithms. In common practice real-time testing of algorithms is done during product development, because research teams at universities are focusing on proof of principle by off-line processing. It is most of the time not in the interest of a research team to perform a real-time implementation. The drawback is that the first real-time implementation is shifted to the product development phase. However, this gives most of the time unexpected problems that cannot be solved by the engineering team. This will cause a delay in product development, since the signal processing implementation has to go back to the research team.

The CVENT PA/US system will be a dedicated **open research platform** with a direct high bandwidth connection of the raw ultrasound signals (RF-data per element) to an external PC. During the CVENT project this research platform (available for the CVENT partners) will serve for research and development on functional PAI and advanced ultrasound beam forming.



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Summary

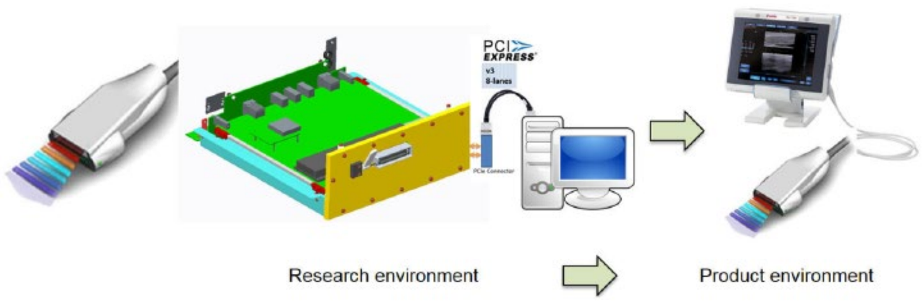
Deliverable 3.3
High Performance Computing Framework (HPCF)

Deliverable 3.3 gives a detailed overview of the ESAOTE "High Performance Computing Framework" (HPCF) to facilitate the research on ultrasound beam forming and advanced PAI signal processing.

The **CVENT research system** for photoacoustic imaging (PAI) will be in use at the CVENT partners as a prototyping platform for:
a) ultrasound beam forming and
b) photoacoustic signal processing. It will also serve as an experimental platform for:
1) in-vitro studies,
2) small clinical in-vivo studies and
3) validation of the different photoacoustic ultrasound probes. Especially the real-time implementation of off-line proven signal processing algorithms will be important for the translation of research into products. In common practice real-time testing of algorithms is done during product development, because research teams at universities are focusing on proof of principle by off-line processing. It is most of the time not in the interest of a research team to perform a real-time implementation. So, the first real-time implementation will be shifted to the product development phase. However, this gives most of the time unexpected problems that cannot be solved by the engineering team. This will cause a delay in product development, since the signal processing implementation has to go back to the research team.

The **CVENT PA/US system** will be developed in different phases. In the first phase there will be a dedicated open research platform with a direct high bandwidth connection of the raw ultrasound signals (RF-data per element) to an external PC. During the CVENT project this research platform (available for the CVENT partners) will serve for R&D. In the product development phase the CVENT proven R&D platform will be integrated in a next generation US platform ready for photoacoustic imaging.

The complete process of implementation, testing, verification, validation and small clinical studies will accumulate in the CVENT PAI research platform. The HPCF strategy will bring real-time imaging under the responsibility of the research teams.



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Summary

Deliverable 3.4

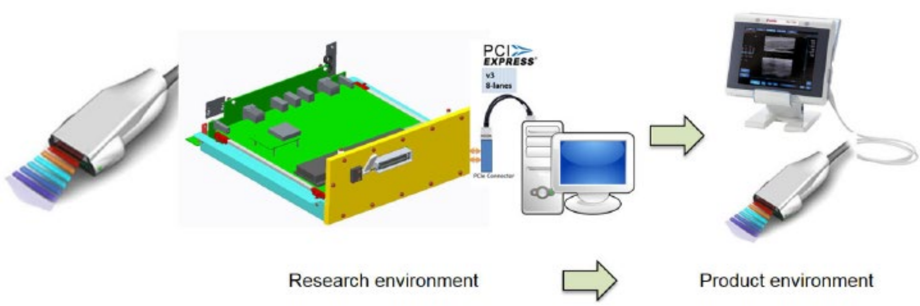
PA/US probe ergonomics

Deliverable D3.4 gives an overview of the integrated safety measures to ensure a proper and safe operation of the CVENT photoacoustic (PA) ultrasound (US) probe. Furthermore, the considerations in relation to PA/US probe ergonomics will be given. The dimensions, size and weight are key factors to be considered in the design of the PA/US probe.

The CVENT photoacoustic imaging (PAI) system must obey certain safety regulations. Apart from the regulations in the Medical Device Directive, here also laser safety aspects play an important role. Hence, the CVENT PA/US probe will have an autonomous integrated control mechanism for enabling the integrated laser source:

- The laser can only be switched on after a confirmation by the user that the system can be used safely and that the probe is positioned properly on the skin.
- In the PA/US probe there is an integrated skin detection for an extra check on skin measurement position. This detection is additional to the user confirmation and will overrule the user confirmation that it is safe to start a measurement.
- The laser can only stay active if the PA/US probe will stay in a certain orientation in relation to the place of measurement.
- The laser will be switched off if the PA/US probe moves away from the skin or if the probe leaves a certain volume in relation to the measurement place or if the user stops the measurement.
- The duration of a single measurement session will be limited to a maximum of 5 minutes. A next measurement session can only be resumed after a certain time-out (30 sec).

The autonoms knowledge about relative position and skin detection - being a probe awareness system - is based on the PA/US probe integrated sensor platform



The research platform with a direct high bandwidth connection of the raw ultrasound signals (RF-data per element) to an external PC will serve as an open low level controllable research and product development platform.

FACTS

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Summary

Deliverable 4.1

Clutter and noise reduction algorithms

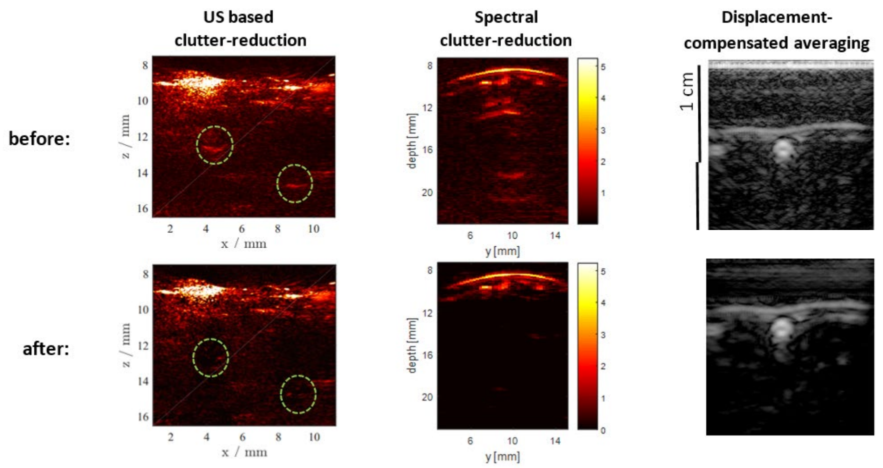
This deliverable D4.1 gives an overview of the methods and algorithms that were developed within CVENT to mitigate the influence of clutter and noise, both of which severely harm image quality and penetration depth.

Since many algorithms require high quality reflection ultrasound data, the first step was to circumvent limited penetration depth due to hardware restrictions of the current photoacoustic-ulrasound-platform MyLabOne. A subsampling filter was implemented for the real-time HPCF framework that exploits the fact that certain band-limited signals can be sampled below the half maximum frequency. The subsampling allowed for twice the penetration depth, or twice the amount of transmit angles for a fix depth, respectively.
Based on this, a displacement-compensated averaging (DCA) method could be realized and already runs in real time in biological tissues.

For fast movements, as present in the carotid artery during pulsation, the frame rate for the current tracking algorithm in DCA was not sufficient. Therefore, a new tracking technique has been implemented.
A clutter reduction technique based on additionally recorded plane-wave acquisitions has been optimized for artifact reduction and bandwidth content under consideration of the temporal transfer function of the transducer. Simulations of the carotid artery predict a promising benefit in the identification of hemorrhages when the clutter reduction technique is applied. A successive application has also been demonstrated in vivo.

In addition, an alternative clutter reduction method has been introduced that relies on spectral correlation of primary PA sources and clutter artifacts. It was shown that the method can successfully identify clutter artifacts in vitro and in vivo.

Finally, the application of adaptive filters in the context of photoacoustic imaging was assessed. While adaptive filters could not be shown to be advantageous over alternative band filters on channel data, it was shown that the SNR during motion could be greatly improved by employing an adaptive filter over multiple frames.
Combining all the above mentioned algorithms, a great improvement of SNR and artefact reduction can be expected, even in the presence of tissue motion, which will allow for long acquisition times and is an important step to reach the required penetration depth.



CVENT clutter and noise reduction algorithms

FACTS

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Summary

Deliverable 4.2

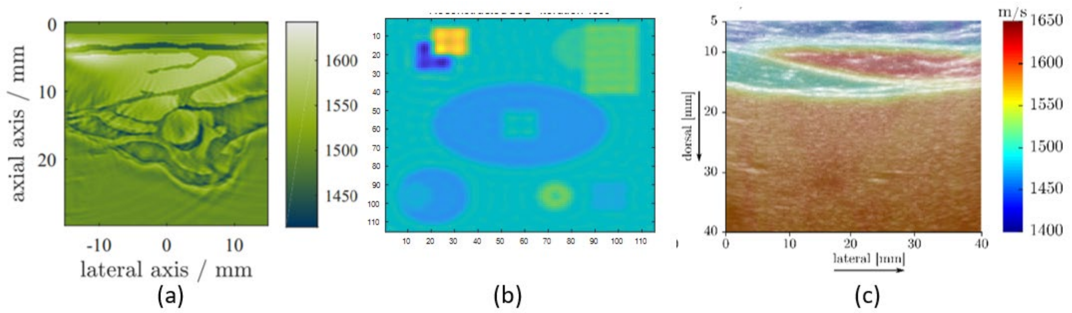
Speed of Sound (SoS) implementation

This deliverable addresses the potential of methods for the quantitative image reconstruction of speed of sound based on ultrasound acquisitions and the question if a hybrid joint reconstruction of speed of sound and photoacoustic source pressure, can benefit the result of each modality. Two strategies were followed. On one hand we investigated nonlinear reconstruction approaches that allow for very accurate estimations of medium properties but are not expected to be applicable in real time. On the other hand, we improved the linear model of a method, which is already real-time applicable.

Two nonlinear approaches were identified as most promising. The first one, known as Kaczmarz reconstruction method, has already been applied to reflection imaging with linear arrays. We assessed if the speed-of-sound (SOS) reconstruction of an area containing the carotid artery and the dimensions of the CVENT probe is feasible in silico. The second investigated nonlinear approach is called contrast source inversion (CSI) that might strongly decrease the computation time but has not yet been investigated for a linear array setup such as used in CVENT. We could already show good reconstruction results of a numerical speed-of-sound phantom for a circular imaging setup. First considerations of how to translate the approach to a reflection-only linear array geometry were discussed and will be assessed until month 36.

Besides reconstructing speed-of-sound distributions for tissue characterization, we also investigated the potential of a hybrid reconstruction that uses knowledge of the speed-of-sound to increase the accuracy photoacoustic imaging. Therefore, we introduced a step-wise photoacoustic reconstruction of medium layers that can account for acoustic scattering. We showed that taking into account the actual speed-of-sound distribution returns similar results to using an estimated distribution returned by the nonlinear Kaczmarz reconstruction, which demonstrates the potential of hybrid reconstruction. Based on these findings, we proposed and discussed a method to include a photoacoustic reconstruction into the CSI approach that will be investigated in the future.

While nonlinear methods have the potential to recover quantitative information, they come with the disadvantage of being very sensitive to model deviations in the actual measurement and require long computation times. Therefore, the linear time-of-flight speed-of-sound reconstruction method CUTE was also further investigated and adapted to the requirements of CVENT. A new forward model was introduced that is more robust against falsely allocated echo positions. Due to problems with decorrelation over the viewing angle, the new model varies both transmit and receive angle. In addition, a new regularization strategy was assessed and the imaging model was further adapted for the aim of imaging the carotid artery despite of blood flow. All enhancements of CUTE were validated in in-vitro or in-vivo studies. In the last months, we will focus on real-time implementation of CUTE.



SOS imaging results, Kaczmarz reconstruction of numercial "carotid artery"-phantom (a), Constrast source inversion result of abstract numercial phantom (b), CUTE results of in-vivo liver image (c)

FACTS

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Summary

Deliverable 4.3 & 4.4

Tissue caracterization & PAI-US elastography

Tissue caracterization

Clutter artifacts and noise negatively affect the photoacoustic (PA) image quality. In deliverables D4.1, methods and algorithms for clutter and noise reduction were reported. This deliverable D4.3 presents an overview of new methods and improvements that were implemented to further enhance the image quality and imaging depth, both in PA and ultrasound (US).
Several different techniques for clutter reduction have been presented in D4.1. Out of these, an approach using multi-wavelength excitation has been reported for in-plane artefact identification. Yet out-of-plane artefacts cannot be tackled with this method. Here we propose a new method using ultrasound transducer array displacement. By displacing the ultrasound transducer array axially, we can distinguish out-of-plane artefacts from in-plane image features and thus remove them. Combining this new method with the wavelength-based technique allows to remove both in-plane and out-of-plane artefacts in photoacoustic imaging.
We further optimized our real-time implementation of displacement-compensated averaging (DCA) for the software that is being used for the clinical feasibility study, and we were able to demonstrate that the CVENT probe is already able to achieve sufficient PA imaging depth to identify the PA signal coming from the carotid artery. In addition we invested substantial effort into improving the US image quality, to aid rapid identification of anatomy and plaque structure using the clinical software.

PAI-US elastography

In patients with a carotid stenosis, US imaging is traditionally used to visualize plaque geometry in patients. Current clinical decision making is based on geometrical criteria (stenosis grade) to determine whether a plaque will be operated upon or not. However, post-surgical data shows that plaque stability or vulnerability does not depend on the plaque shape but on its content (morphology) and strength (mechanical properties).
Two exciting new modalities that can add functional and molecular information to existing geometry assessment are ultrasound elastography and photoacoustic imaging. The former can be used to estimate mechanical properties such as deformation (strain) or elasticity (shear modulus), whereas the latter can be used to visualize which compounds are found in the plaque based on their optical absorption characteristics. The combination of these data has the potential to improve clinical decision making by identifying the vulnerable plaque
In this deliverable of the C-VENT project, methods developed for combined PA and US elastography imaging are presented. Moreover, a framework patient-specific modeling of plaques was introduced, providing valuable artificial data that can be used to validate and verify both elastography and PA/US imaging. The methodology can also be used to build mechanical models of each individual plaque. Motion tracking and strain estimation serves as input for these models, yielding the patient-specific arterial stiffness. In vitro application of the techniques is used for testing and validation of in vivo results.

FACTS

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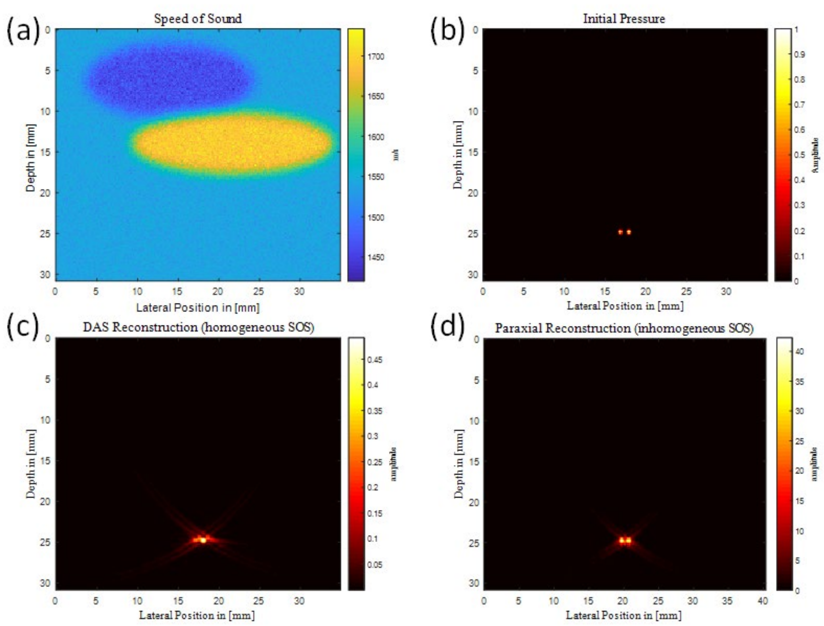
Summary

Deliverable 4.5

Image aberration correction software package for US and PA imaging

This deliverable D4.5 reports on the investigated methods available for aberration correction of photoacoustic (PA) images. The focus is especially on the paraxial backpropagation used for a fast photoacoustic reconstruction in acoustically heterogeneous media that has been developed within CVENT.
The paraxial backpropagation is a known approach in ultrasound tomography and has already been used in both transmission and reflection ultrasound tomography (1,2). Transferring this technique to PA imaging offers a new possibility to improve image quality by reducing aberration artifacts since the speed of sound of the investigated tissue region can be accounted for. Since the ability of reducing aberration depends on the speed of sound (SOS) distribution which serves as input for the investigated methods, several scenarios were examined.

First, reconstructions with the standard assumption of a homogeneous medium were done. Then, photoacoustic reconstructions using the true SOS distribution were performed which serve as a reference representing the full potential of the aberration correction capability of the algorithms. In practice, the SOS distribution is an unknown function that must first be reconstructed. Here, in a separate experiment, we derived the SOS estimate using computed ultrasound tomography in echo mode (CUTE) developed further within CVENT, which is then taken into account for the aberration correction techniques. Aberration correction is tested both in a simulation study and on data of a tissue mimicking phantom acquired with the CVENT probe.



Aberration correction simulation study.
(a) True SOS distribution,
(b) Initial pressure distribution to be reconstructed,
(c) Standard delay-and-sum reconstruction without considering the SOS distribution,
(d) Reconstruction result of the paraxial backpropagation approach with incorporation of the true SOS distribution

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Summary

Deliverables 5.1 & 5.2

Plaque testing setup (5.1) & First in-vitro results (5.2)

Plaque testing setup
In the C-VENT project new imaging systems and techniques are developed. Before applying these methods in men, experiment testing is required. This deliverable (D5.1) gives an overview of the experimental framework developed at TU/e.

A setup for experimental testing of photoacoustic (PA) techniques was developed. The setup allows imaging of photoacoustic phantoms (mimicking arteries and their constituents) and arteries obtained from surgery.

The setup consists of a piston pump that can be used to pressure the phantom/artery or provide flow. The samples, collected from a local hospital after the patient's consent, are mounted in the middle. Water is added to allow for PA/US imaging. The sample can be rotated 360 degrees to get a full view of the artery with optimal image quality. Next the PA/US probe is moved in the third direction, along the vessel's axis, to create a 3-D volume scan.
Phantoms were developed of simple rubber-like material (PVA) that have the same elastic and acoustic properties as arteries. Typical material that you would find in a plaque, such as fresh blood, clotted blood (= haemorrhages), and cholesterol (= lipids). PA/US imaging was performed to get optimal images, but also in less optimal settings when surrounding (light absorbing) tissue was present. Moreover, histology was done on the samples after the PA/US testing to verify the PA/US images.
This platform is now available for samples coming from our intra-operative study and will help testing, verifying and clinically validating all techniques developed in this project.

First in-vitro results
Using the new PA/US system and the setup shown in D5.1, the first phantoms and samples were tested. The use of PA/US to detect intra-plaque haemorrhages, fresh blood and lipids was tested using a rubber-like vessel phantom with three inclusions that contained the aforementioned tissue types. Secondly, a phantom was introduced with both haemorrhages and channels with flowing blood (mimicking the vasavasorum), where microchannel flow was added in the artery wall. These methods were images using the C-VENT system and nicely showed the ability to separately detect different materials or the difference between flowing blood and static blood (= hemorrhaeges).
Next, plaques were imaged. Blind unmixing showed the ability to detect haemorrhages and distinguish between fresh and mature ones. Histology confirmed our findings. Next steps will be to validate the penetration depth of the C-VENT system and use the system in vivo.

FACTS

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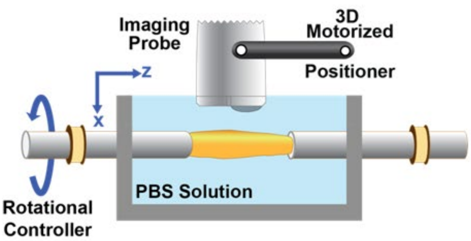

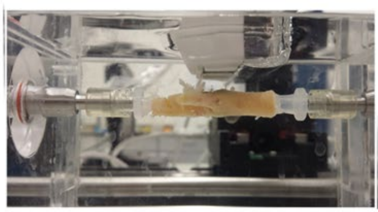

Setup design: plaques are mounted between to steel rods, connected to a rotational controller.
The probe can illuminate the vessel from the top, and is connected to a 3-D motorized stage.

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Summary

Deliverables 5.3 & 5.4

In-vivo pilot study finalysed (5.3) & *In-vivo* and *in-vitro* study (5.4)

In patients with a carotid stenosis, US imaging is traditionally used to visualize plaque geometry in patients. Current clinical decision making is based on geometrical criteria (stenosis grade) to determine whether a plaque will be operated upon or not. However, post-surgical data show that plaque stability or vulnerability does not depend on the plaque shape but on its morphology, i.e., the presence of a large lipid pool, intraplaque hemorrhage and macrophages. Identification of intraplaque haemorrhage using magnetic resonance imaging (MRI) is expensive, technically demanding and sometimes uncomfortable. Photoacoustic imaging (PAI) is a new non-invasive technique combining multi-wavelength infrared laser light and ultrasound (US) imaging, able to discriminate blood and other components in the tissues. The measurement by the multi-spectral PAI is likely to be more applicable and therefore could be complementary to MRI. In this deliverable of the CVENT project, it was aimed to validate a portable multimodal and multi-wavelength PAI system, for the identification of intraplaque haemorrhage and compare with MRI and histology.

In-vivo and in-vitro study

The results of the two *in-vivo* studies are presented, executed in Eindhoven and Paris. Measurements were performed using the CVENT, fully integrated, laser-diode-based photoacoustic probe. The Eindhoven study was a pre- and intraoperative study, where PA / US imaging was applied non-invasively, and compared to first-time intra-operative measurements using the first CVENT system.
The second study, performed in Paris, was focused on non-invasive imaging. PA / US results are compared to MRI. In both studies the excised plaques were subjected to a histological analysis.
Results of the Eindhoven study showed the potential of PAI in the intraoperative setting (N = 16), detecting intraplaque hemorrhages that were also found in histology. Several advances in the signal enhancement were implemented to up the penetration depth, needed for *in-vivo* PAI. The optimized system was successfully used on 25 patients in Paris. Here, PAI showed to be able to identify histological intraplaque hemorrhage with a good to excellent level of specificity and an acceptable sensitivity, equivalent to MRI for plaque detection.

Large scale studies to investigate long-term prognosis of individuals with intraplaque hemorrhage and no indication to carotid surgery are needed, combined with experimental verification.

FACTS

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Summary

Deliverables 6.1 & 6.5

CVENT public website (D6.1) & project video and training (D6.5)

Dissemination and exploitation of project results are an obligation for every Horizon 2020 beneficiary. Horizon 2020 funding is obtained via taxpayers' money: therefore, the investment made by the European Union must be converted into socio-economic benefits for the society as a whole, in a transparent and accountable way.

Public website
Communication means taking strategic and targeted measures for promoting the action itself and its results to a multitude of audiences, including the media and the public. All CVENT partners commit themselves to make every effort to communicate information concerning the project and its progress to an as wide audience as possible. The main CVENT communication tool towards the public is the website http://www.cvent-2020.eu. It is intended to inform the public about the project and to promote the CVENT technology towards the public and also to attract young pupils and students.

Project video
A PR video (D) on CVENT development and application has been produced by TP21 and the partners. The motivation is presented by TUE, the concept by the coordinator. They explain the medical need for the device and their technology and how this technology will contribute to the integrated system. Partners give insight in their facilities and workspaces. The video is available via the public website www.cvent-2020.eu and will be presented at exhibitions on partners' booths. Subtitles are available for mute presentations.

Online trainings
The CVENT consortium will offer publication-based trainings. Short videos will present and explain the latest results of the CVENT project research. These videos will be promoted via the project website and platforms as LinkedIn and facebook. At the same time, CVENT students will learn how to communicate scientific projects to the general public. The authors will give some background information on the scientific question investigated. A link to open access publications will be provided for each training topic connected to the video to ensure up-to-date training sessions with high quality content and results.

Sequences overview CVENT project video

FACTS

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Summary

Deliverables 6.2, 6.3 & 6.9

Three internal training workshops

The CVENT consortium unites leading research groups, clinicians, industrial partners, and their expertise on research and development. The consortium will focus on exploitation and creating a breakthrough in carotid plaque vulnerability diagnosis. Moreover, CVENT will bring together leading experts in the field of CVD, functional US imaging and PAI, introducing clinically applied PAI into the vascular medical arena.

The successful development of photo acoustic equipment for revolutionary diagnostic approach for screening, in-depth diagnosis and monitoring of carotid plaque vulnerability requires expert knowledge and the close cooperation of a variety of scientific disciplines. In the CVENT project, there is a direct cooperation and interaction between clinicians, acting day-by-day in the related vascular medical field, system engineers and researchers on PAI signal processing, and product developers creating an efficient translation from research to verified and validated product development.

Due to the high degree of interdisciplinarity, several internal workshops are held to build up a broad joint knowledge on different core technologies important for the project.
CVENT partners already collaborated in the FP7 FULLPHASE project - Fully integrated real time multi-wavelength photo acoustics for early disease detection (No. 318067) with several internal workshops on the relevant technologies on the component level i.e. on laser technologies, diffractive optics, ultrasound imaging, and photoacoustic imaging. Therefore, the CVENT workshops focus on medical applications, given by physicians (1st workshop), the Medical Resonance Board (MRB) members (2nd workshop) and academic partners on signal processing algorithms.

The 1st workshop on stroke and vulnerable plaques provide a joint knowledge base to the consortium and on the clinical validation processes. These talks open the discussion and trained the consortium in clinical validation requirements for the upcoming device specification work of the engineers and scientists.

The 2nd workshop was held by three physicians: A specialist in cardiology, clinical pharmacology and nuclear medicine, a Neurologist and a stroke specialist.

The 3rd workshop focused on real-time implementation of the photoacoustic imaging (PAI) signal processing algorithms.

CVENT prototype demonstration

FACTS

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Summary

Deliverable 6.4
First dissemination and exploitation plan

CVENT want to create awareness in the society and the scientific and medical community on the great opportunities and advantages of the new technology for a successful marketing and exploitation of the CVENT development and results. The knowledge and competencies to be developed in the CVENT project is resulting in a multitude of innovation and marketing opportunities especially for the industry partners involved in the CVENT project. The developments are offering potentials for a technology transfer beyond the applications envisaged in this project. CVENT could have a significant impact since the medical device market is rapidly growing. In particular, the market of laser-based devices for diagnosis and therapy, which is presently dominated by American companies, is a challenge for innovative European enterprises.

Dissemination is a key activity for achieving the CVENT objectives and materialising its expected impact, by informing about work progress and the results obtained. Implementing a successful dissemination strategy requires that the goals, as well as the target audiences, are clearly defined.
CVENT dissemination aims at:

- Raising interest among the vascular medical community and vascular surgeons.
- Communicating the achievements of the project amongst SMEs to improve their access to CVENT results.
- Communicating CVENT novel decision support system to responsible health system stakeholders Training and inform vascular medical community and vascular surgeons, the CVENT PAI system end-users.
- Creating awareness towards the public on CVENT.

Both, academic and industrial CVENT partners therefore decided on a strong dissemination strategy that includes conference contributions, peer reviewed publications, and training sessions to inform and train the specialist, mainly provided by the academic partners. Further dissemination tools are promotion material as a project website and video, press articles to different audiences, and a social media campaign with the possibility of simplifying the message to make it reachable by the public.

CVENTS's dissemination and exploitation plan considers three levels of actions:

- An internal confidential level related to information and actions communicated and used only by the project's partners
- An external restricted level comprising actions and material directed towards the medical/scientific/industrial community and
- An external public level of communication directed to further stakeholders and the general public.

The CVENT dissemination categories are promotion, information and training to different audiences.

FACTS

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Summary

Deliverable 6.6
First exploitation report and IPR plan

Due to the ageing population the request for a change in healthcare delivery becomes inevitable. As people live longer the number of hospitalizations and clinical interventions rises. This upcoming increasing necessity for medical care is underlining the need for a cost effective change in healthcare delivery. Key items in this process of change are early disease detection, improved diagnostics and advanced treatment monitoring all by means of point-of-care functional imaging.

Within this context, the focus of CVENT consortium is on the translation of photoacoustic imaging (PAI) from a research-based image modality to a high performance low-cost portable multi wavelength combined PAI system for vulnerable plaque imaging. Cardiovascular disease (CVD), more specifically, vulnerable plaque rupture, remains the major cause of death for people at middle age. In the carotid arteries feeding the brain, vulnerable plaque rupture initiates cerebrovascular ischemic attacks. Consequently, there is a worldwide unmet and urgent clinical need for functional information to enable in-depth diagnosis of carotid plaque vulnerability, avoiding cardiovascular events (CVENT).

The objective of the CVENT consortium is the development of a portable multimodal and multi-wavelength PAI system, for diagnosis and monitoring of carotid plaque vulnerability. The combination of high optical contrast of PAI and the high resolution of US will be used to identify plaque vulnerability markers, typically lipid pools and intra-plaque haemorrhage. Improved diagnosis of carotid plaque vulnerability will lead to a significant reduction in CVD-related disability and mortality. Simultaneously, by stratifying patients into high and low risk groups, overtreatment is reduced, leading to better allocation of healthcare funds.

The CVENT strategy intertwines beyond-state-of-the-art R&D with strong stakeholder involvement and clear exploitation paths by the industrial partners. The specific guiding principles will be:

- Close involvement of physicians, from requirement specifications to the validation of the CVENT PAI system.
- Short feedback loops between:
  1) medical practice,
  2) engineering and
  3) advanced signal processing during the R&D process.
- R&D on a highly sensitive PA/US probe and signal analysis/enhancement methods that warrant sufficient penetration depth and signal-to-noise ratio for in-vivo plaque imaging in the carotid artery.
- Validation of the CVENT PAI system in experimental and clinical settings to support an efficient translation, from research towards product development and clinical application.
- Active communication with stakeholders and our medical resonance board to create awareness for the CVENT approach.

The CVENT PAI system will provide a revolutionary diagnostic approach for screening, in-depth diagnosis and monitoring of carotid plaque vulnerability. As a result, it will open an additional market on vascular ultrasound for ESAOTE. The strong industrial participation in the CVENT consortium will, next to the exploitation of the PAI system in the medical field, create strong exploitation opportunities for the CVENT system components. Specifically, these are: ultra-high power pulsed diode laser (QUANTEL), high efficient diode laser drivers (BrightLoop) and advanced diode laser diffractive optical beam forming (SILIOS).

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Deliverable 6.7

European CVENT technology transfer event

The CVENT Exhibition at the ARTERY international conference took place in Budapest, Hungary, from October 10th to 12th, 2019. The Artery conference is dedicated to the study of arterial structure and physiology and is frequented by a highly informed audience. Most of the audience are clinicians who are interested in the arterial structure, focusing on the aorta, carotid, and peripheral arteries. The CVENT project was presented in three different manners during this conference. Firstly, the final CVENT probe design with clinical preliminary results was presented at the CVENT booth, showing the comparison between the CVENT probe results and MRI data via a slideshow of pictures. The 2nd CVENT video concerning the ongoing clinical studies in Paris (UPD) and Eindhoven (TU/e) was displayed at the booth. This video targets on the general public and is more diagnosis oriented, whereas the first video was science and development oriented.
In addition, a banner was visible that informed on the project, as well as displaying the project logo as well as the EU funding acknowledgement. Hand-outs on the project were also distributed to the visitors of the conference.
Booth staff: Peter BRANDS (ESAOTE) & Hasan OBEID (UPD).
Secondly, Dr. Richard LOPATA (TU/e) gave an oral presentation in the main amphitheatre, the main location, at primetime. The 30 minutes talk on 'Novel imaging techniques of arteries' was followed by a 15 minutes discussion with the audience. The main topic was about the photoacoustic technique to image carotid arteries, including the development of and integration in the CVENT probe, and an overview of the preclinical studies at TU/e and UPD. Results in terms of images highlighted the efficiency of the CVENT probe to detect carotid plaques with strong PA signals coming from the plaque which correlated to the presence of carotid plaque haemorrhages.
The feedback of the audience was very positive and enthusiastic. Dr. Lopata was asked several questions regarding the system, the outlook on multi-constituent imaging, and on the clinical implementation of the technique.
Thirdly, a CVENT poster was presented by Yuki IMAIZUMI (UPD) in the clinical aspects poster session. The poster contained the first results acquired with the final probe design. The CVENT medical resonance board (MRB) members had been invited by Prof. Pierre BOUTOUYRIE (UPD) to visit the booth at the conference. The feedback in general was positive: The MRB members were very interested in the project and the novel technique used.

CVENT presentation at ARTERY 2019 in Budapest - facebook post

FACTS

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