White Paper

Vascular Biomarkers in Cardiovascular Risk Prediction

& Radiofrequency-based Vascular Ultrasound Technology

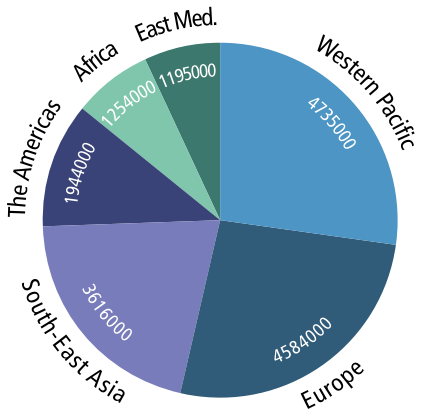
esaote
Creativity in Healthcare

- Radiofrequency signal-based technology of ESAOTE (QIMT and QAS) facilitates the utilization and interpretation of vascular biomarkers in clinical practice
- QIMT offers superior accuracy and reproducibility of measurements due to its high spatial resolution and real-time feed-back on exam quality
- QAS with its high temporal resolution provides the possibility of accurate estimation of local arterial stiffness, local pulse pressure and local PWV
- QAS and QIMT combined with standard B-mode-Doppler US allows a multifaceted evaluation of vascular structural and functional impartment during a single exam
- "Normalcy values" of QIMT and QAS measurements obtained in a large European population facilitate an interpretation of exam in each individual subject

Cardiovascular Diseases and Prevention

Cardiovascular disease (CVD) is the leading cause of death worldwide. According to the World Heart Federation, about 17.5 million of people die each year from CVD (Figure 1). The corresponding numbers for the Europe and the European Union are 4.5 million and 1.5 million, respectively (data of the European Society for Cardiology).

Figure 1 Total number of death due to cardiovascular diseases worldwide (17 327 000)



Due to an increase in life expectancy, the medical cost of CVD increased in the past years at an average annual rate of 6%. In 2012, overall cardiovascular disease was estimated to cost the EU economy € 196 billion a year, and the US economy $ 273 billion a year. The cost is expected to further escalate in the next 20 years.

CVD is largely preventable, and indeed, it is estimated that 80% of premature heart disease and stroke could be avoided. The success of primary prevention depends on the accurate identification of subjects who are at risk of future cardiovascular events. Various risk scores (Framingham Risk Score, SCORE Charts) have been developed to guide the preventive strategies, yet these scores estimate a population-based risk rather than quantifying the individual risk. Furthermore, a substantial part of population belongs to intermediate risk, where it is not clear whether aggressive prevention strategy is beneficial and cost effective.

Role of Vascular Biomarkers in Cardiovascular Risk Assessment

The use of cardiovascular biomarkers in conjunction with risk scores is expected to refine the risk stratification of an individual subject and to guide his therapy. Biomarker is a characteristic that is objectively measured and that reflects early functional and structural changes in cardiovascular system, before overt disease manifestation. Vascular biomarkers may be particularly informative, as they detect organ damage in different parts of vascular bed, are measurable in a non-invasive way, and reflect both aging process and adverse impact of established cardiovascular risk factors, like plasma lipids, smoking, high blood pressure, diabetes, inflammation[1-2].

Nowadays, several vascular biomarkers have been proposed. According to a position paper from the European Society of Cardiology Working Group on peripheral circulation, the choice of vascular biomarker or a combination depends on the clinical setting and present comorbidities, and may differ for each individual patient[3].

Requisites of Biomarkers

Biomarkers should satisfy several steps of validation that should verify if the biomarker differs between subjects with and without outcome, if it predicts the development of future events over and above established risk markers, if its change predicts the risk sufficiently to change the therapy, and if its use improves clinical outcomes[4]. Furthermore, biomarkers should be relatively **easy to measure**, the measurement technique should guarantee **adequate accuracy and reproducibility**, and for each measurement the **reference values** should be available[3]. Such characteristics permit a widespread application in daily practice.

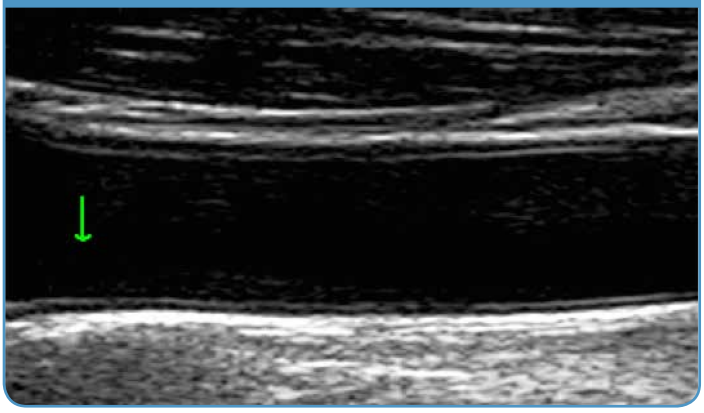
Radiofrequency Signal-based Vascular Ultrasound

Vascular ultrasound of ESAOTE employs radiofrequency (RF) signal-based technology and includes Quality Intima-Media Thickness (QIMT) measurement and Quality Arterial Stiffness (QAS) measurement.

A RF signal is a reflected US signal that is captured by the transducer and converted in an electric signal preserving all the characteristics of the acoustic wave in terms of Amplitude and Phase. A consequent elaboration of RF-signal waveforms into a bi-dimensional video-image includes conversion to grey-scale format with significant reduction of dynamic range, subsampling to fit the video-image height, and a lost of information regarding the Phase. For these reasons a video-based system could never have the accuracy of a RF-based system.

Quality Intima-Media Thickness (QIMT)

Figure 2 B-mode image of normal common carotid artery with a thin intima-media layer

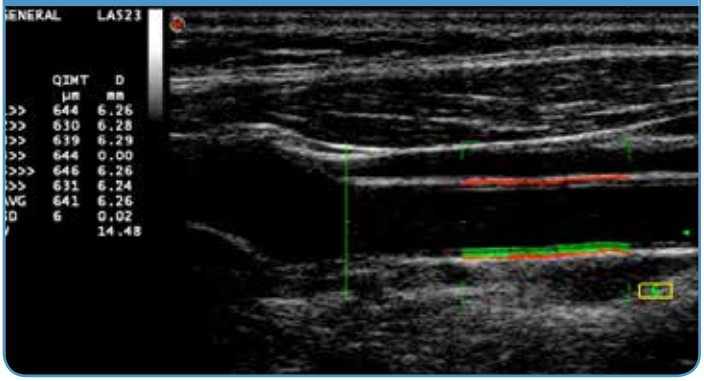


Accuracy of QIMT measurement

In healthy subjects, an average IMT ranges between 400-750 µm (Figure 2), and IMT progression rate between 6-10 µm per year[2,5-7]. Therefore, a high accuracy is mandatory to measure the IMT and, above all, its changes.

Within the 1-cm long ROI, in which far-wall IMT is measured, (Figure 3), the number of RF samples is higher (more than 400) than pixels in the corresponding video-image (about 50), and therefore, the spatial resolution and accuracy of RF-based system is considerably superior.

Figure 3 QIMT examination. Far-wall CCA IMT is automatically measured within the ROI (green rectangle). The values of IMT and diameter (D) are displayed beat-to-beat on the screen, and the mean value (AVG) over the last 6 beats and standard deviation (SD) are continuously calculated



An appropriate measurement of IMT according to Mannheim protocol[8] is further facilitated using QIMT technology (Figure 3). The vertical green line positioned at the beginning of carotid flow-divider guarantees an automatic measurement of far-wall IMT within a 1-cm long segment starting 1 cm before the flow divider. Furthermore, QIMT provides an operator with a real-time feed-back on measurement quality, as a table on the left side of the screen displays IMT and diameter values over the last 6 cardiac cycles, together with average value and SD. Good-quality QIMT measurement is obtained with low SD (lower than 10-15 µm) and a fully displayed green overlay on the carotid far wall (Figure 3).

QIMT reference values

The interpretation of IMT values and their relevance in cardiovascular risk assessment has been hampered by the absence of reference values. Elaboration of data obtained by Esaote RF-based system in 24 871 men and women worldwide[5], permitted to establish sex- and age-specific percentiles of common carotid artery IMT (in the sub-population of 4 234 healthy individuals), together with Z scores allowing a standardized comparison between observed and predicted ('normal') values from individuals of the same age and sex. These data should facilitate the interpretation of IMT data in individual subjects.

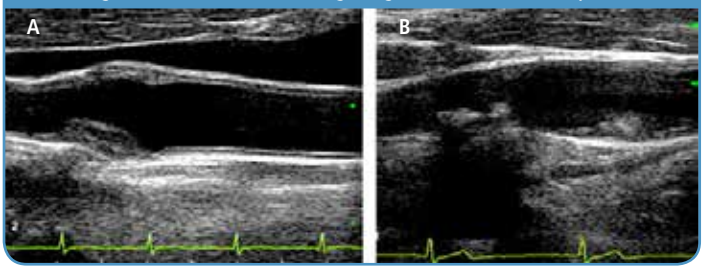
IMT as vascular biomarker

The European Society of Hypertension/European Society of Cardiology guidelines for the management of hypertension[9] have endorsed carotid IMT measurement (class IIa/B) in patients with high blood pressure. The Society of Cardiology guidelines[10] for cardiovascular disease prevention recommended carotid IMT measurement in individuals at intermediate risk (class IIa/B).

Carotid plaque as vascular biomarker

RF-based technology of Esaote is implemented in a standard US system, and therefore, a standard B-mode-Doppler US of extracranial carotid tree can be also performed, allowing the detection of carotid plaques (Figure 4) and quantification of carotid stenosis.

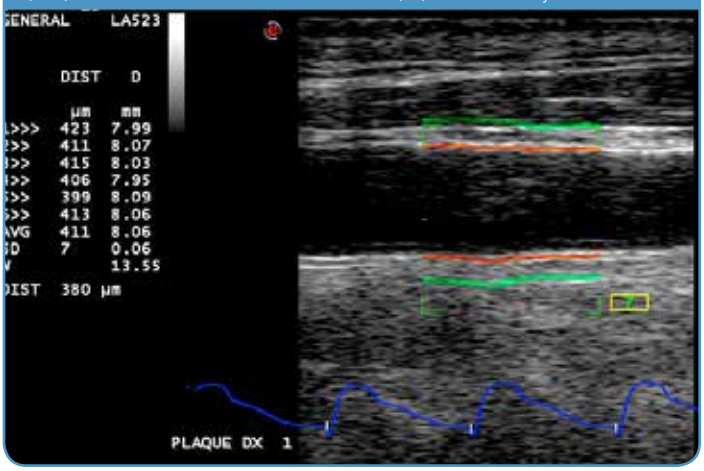
Figure 4 A) Soft concentric plaque in carotid bulb; B) Irregular plaque with US shadowing in carotid bulb and in the beginning of internal carotid artery



The presence of carotid plaques alone or in combination with IMT, has been shown to predict cardiovascular death and events independently of the SCORE and Framingham risk score stratification[11-12].

Quality Arterial Stiffness (QAS)

Figure 5 QAS examination in healthy subject. The movement of carotid walls is tracked in the entire ROI (green rectangle) composed of 32 scanning lines. Continuous red lines indicate the automatic positioning of wall tracking points at media-adventitia interface. Continuous green lines display dynamically the amplified vessel wall movement. Real-time distension waveforms are displayed at the bottom (blue line). The values of carotid distension (DIST) and diameter (D) are displayed beat-to-beat on the screen, and the mean value (AVG) over the last 6 beats and standard deviation (SD) are continuously calculated.

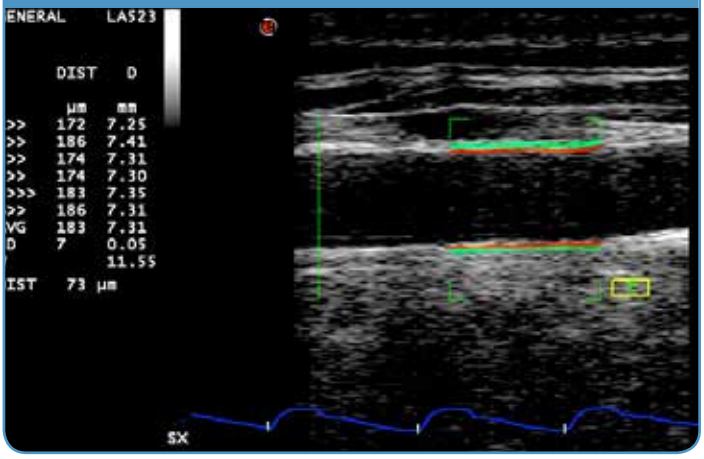


Accuracy of QAS measurement

Local arterial stiffness is estimated as systo-diastolic changes in arterial diameter/area over systo-diastolic changes in distending pressure (pulse pressure). QAS, thanks to its high frame rate and RF signal resolution, is capable to follow the movement of the arterial wall throughout the cardiac cycle with a great accuracy. From the real-time distension curves (Figure 5-6), maximum and minimum carotid diameters are measured, and arterial distension is calculated.

Local distending pressure is estimated converting the distension curve to pressure curve by a linear conversion factor and assuming that the difference between mean arterial pressure and diastolic pressure is invariant along the arterial tree[13]. From arterial distension and local pressure, number of stiffness parameters is automatically calculated, including local carotid pulse-wave velocity (PWV; Bramwell-Hill equation[14]). QAS technology can be applied to ascending aorta, carotid artery, brachial artery and femoral artery, thus allowing to investigate the impact of different risk factors on both elastic and muscular arteries.

Figure 6 QAS examination in diabetic patient with significantly reduced carotid distensibility.



QAS reference values

Elaboration of data obtained by Esaote RF-based system in 22 708 individuals (age 15-99 years) from 24 research centers worldwide[15], permitted to select 3 601 healthy individuals, in which sex- and age-specific percentiles of common carotid artery stiffness (Figure 5), together with Z scores, were established. These data enables a comparison of carotid stiffness values between patients with different cardiovascular risk profiles, thus facilitating the use of this biomarker in clinical practice.

Similar elaboration was performed also for the muscular femoral artery (N = 5 069)[16]. In contrast to elastic carotid artery, the stiffness of femoral artery in healthy sub-population (N = 1 489) does not change substantially with age up to the sixth decade.

Arterial stiffness as vascular biomarker

Carotid-femoral (cf) PWV measuring a segmental aortic stiffness is the most validated approach for arterial stiffness assessment. Cardiovascular events increased by 30% per 1-SD increase in cf PWV[17], and its predictive value retains after adjustment for Framingham risk score or SCORE[18]. Local carotid and femoral stiffness measurement were introduced to clinical practice much later, with RF-based technology, and their validation as biomarkers is still in progress. A recent prospective study has shown that in a population-based cohort (Hoorn Study) followed-up for 7.6 years, the hazard ratios for cardiovascular events and all cause mortality was 1.22 and 1.51 for lower carotid distensibility, and 1.39 and 1.27 for lower femoral distensibility, and these values were comparable with those for higher cf PWV (1.56 and 1.13, respectively)[19].

Conclusions

A widespread use of vascular biomarkers in daily practice of specialists working on the field of hypertension, diabetes, obesity and other conditions contributing to the CVD risk, requires technology that is relatively easy to perform and, at the same time, guarantees appropriate accuracy, reproducibility and interpretation of measurements. RF-based vascular technology of Esaote, which guides the operator and provides real-time feedback about the quality of examination, allows to perform accurate, reliable and quick IMT measurement even by operators not expert in cardiovascular ultrasound. Furthermore, the possibility to measure, during the same examination and by the same technology, also a carotid or femoral stiffness increases the probability to detect early organ damage, understand the pathophysiology of vascular changes and thus, to improve the assessment of individual risk and decision-making regarding the life-style or therapeutic interventions. At last, but not at least, the unique availability of sex- and age- specific percentiles and Z-scores facilitates the interpretation of IMT and stiffness measurement.

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