Comparison of Extrinsic and Intrinsic Dynamic Contrasts in Fast 3D Optical Mammography

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Abstract: We compare the performance of dynamic DOT of the diseased breast for intrinsic contrast (Valsalva) and external contrast agent (ICG). Both show similar signal strength but reproducibility and diagnostic power is greatly enhanced with ICG.
OCIS codes: (170.6960) Tomography; (170.3830) Mammography; (170.6935) Tissue characterization

1. Introduction

Recently, it has been demonstrated that the exploitation of dynamic contrast features in diffuse optical tomography (DOT) of the breast can greatly enhance the diagnostic power when compared to imaging static contrasts [1-3]. The main reasons are twofold; first, the imaged hemodynamics are intrinsically linked to the local tissue physiology and pathology and therefore serve as sensitive correlates for a wide range of disease states. Secondly, the image reconstruction of dynamic features greatly stabilizes the inverse problem, and signal extraction strategies can isolate the dynamic features of interest from background noise, thereby enhancing the signal-to-noise-ratio. As an added benefit of these last features, less stringent demands are also posed on the imaging equipment in terms of the required accuracy (no need of absolute measures) and stability (less demanding on drifts).

Dynamic features that have been investigated include tissue-intrinsic dynamic such as the resting auto regulatory rhythms or breathing maneuvers as well as those evoked by external contrast mechanism such as the application of tissue pressure, the use of non-air breathing gases or use of blood-borne dyes [1,4,5]. While intrinsic contrasts have the advantage of generally being easier, less costly, and safer to apply when compared to external contrast application, the latter often provide better replicability of the effect, promising an improved diagnostic performance.

In the current study we compare the diagnostic performance of the measured response to a Valsalva maneuver with that of a signal transient following ICG bolus injection.

2. Methods

We used a DYNOT 232 optical tomography imager (NIRx Medical Technologies, NY, USA) with a custom patient bed and fiber holder, the details of which are described in [1,2]. The system performs full tomographic scans of 31 co-located illumination and detection points on the breast at a rate of approx. 2 scans per s at simultaneous 760 nm and 830 nm illumination.

Under ethical approval of the hospital's ethics committee, we recruited 22 patients who had a high probability of a breast lesion and who were scheduled for needle biopsy. Of these, we included in the analysis 14 patients with a malignant lesion and 7 patients with benign lesions. Patients were instructed and trained on the breathing protocol and, after initial rest, were asked to perform a series of three Valsalva maneuvers (forced expiration against the closed glottis for 15 sec.) in 3-min intervals. After 5 min following the last maneuver, we administered a single bolus of 25 mg ICG (Pulsion AG, Munich, Germany) dissolved in 15 ml *aqua ad injectionem* (injection time: 5 sec), flushed by 15 ml of saline solution.

Data were preprocessed and reconstructed using NIRx NAVI software (Near Infrared Analysis, Visualization and Imaging, Rev. 8.11 by NIRx), which was run under MATLAB (The Mathworks, Inc., Natick, MA). Data were first first low-pass filtered (f_{cutoff} ~0.075 Hz) and then normalized to the temporal mean value during the initial resting phase. Channels exhibiting too much noise (coefficient of variation > 25%) during the rest phase were excluded. The reconstruction of 3D time series of relative concentration changes over a total of 2243 volume segments covering the entire breast cup utilized the normalized-difference as described in [3]. For the time-based analysis, the time of bolus arrival t_0 was defined as the earliest time at which > 0.25% of the breast volume has reached the peak amplitude.

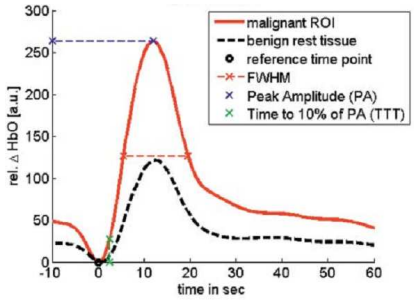

Figure 1. Example of the volume-averaged *Δ*HbO response to the Valsalva maneuver for healthy and diseased tissue.

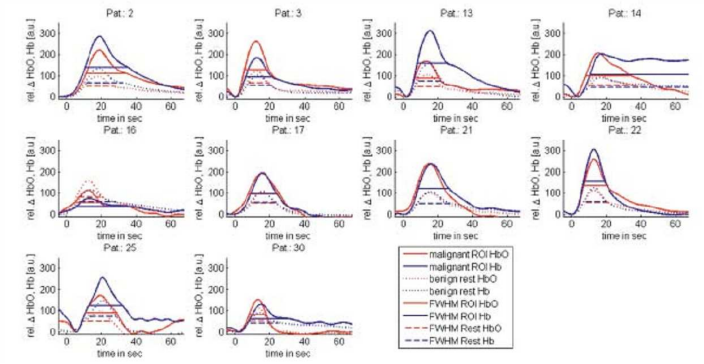

Figure 2. Individual responses to Valsalva maneuver for the 10 patients with malignant lesion.

3. Results

Valsalva Maneuver

Fig. 1 shows the exemplary spatially averaged relative HbO change in response to a Valsalva maneuver in both diseased malignant tissue and the healthy background. In both Hb states, the malignant tissue tends to show greater response amplitude, faster rise time, and temporally elongated response compared to healthy tissue. This behavior is consistent with the well-known functional and structural deficiencies of the neo-angiogenetic vasculature formed by tumors [6]. To account for inter-subject variation, and to provide quantitative measures, we investigated three metrics as indicated in Fig. 1: (1) full width at half maximum (FWHM), (2) 'time to ten' (TTT), i.e. the rise time the signal takes to reach 10% of its maximum, and (3) peak amplitude (PA).

Fig. 2 shows the Valsalva responses for all patients with a malignancy. Although a clear tendency exists for the malignant tissue to display a faster rise, higher amplitude, and longer response, the significant inter-subject variation of the response is evident. To evaluate the diagnostic value we created spatial maps of the above described metrics (Fig. 3) and provided these to two trained readers who were asked to decide whether and how many malignant lesions were present. The sensitivity was highest for PA (70-80%) and only in the 50-60% range for TTT or FWTH. The specificity, however, was low overall and, incidentally, lowest in PA (10-20%); for TTT and FWHM specificity was in the 30-45% range.

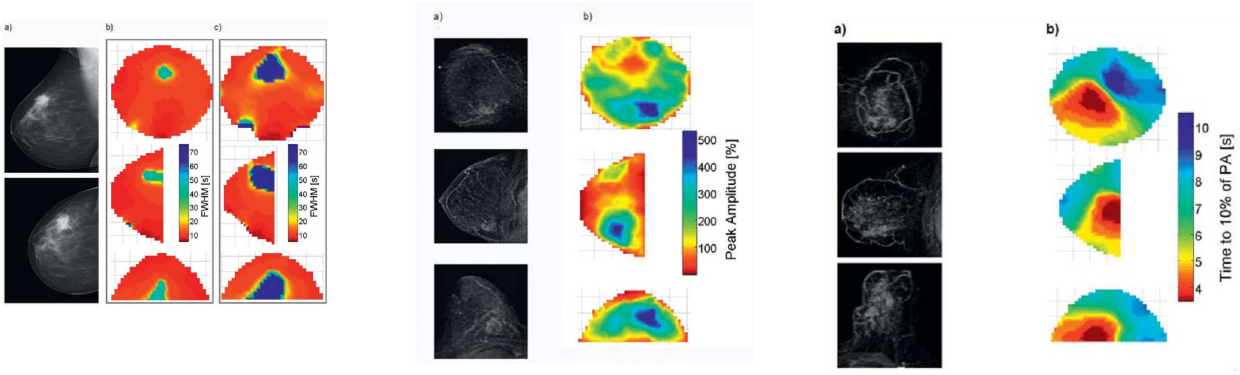

Figure 3. Example for the optical metrics maps derived form the Valsalva data in comparison with Gd enhanced MRI findings for malignant cases. Left: FWHM map for patient with 27-mm invasive ductal carcinoma (b) HbO, c) HbR) Center: PA image for 26-mm IDC patient (HbO). Right: TTT map for patient with 80-mm ductal carcinoma in situ (HbO).

ICG Bolus

Fig. 4 shows the volume averaged optical response to the ICG injection for the malignant and the healthy breast compartments. The malignant tissue again shows an exaggerated response that is characterized by a fast increase, higher PA, and elongated decline. For the diagnostic analysis we created a composite metric that for each time point

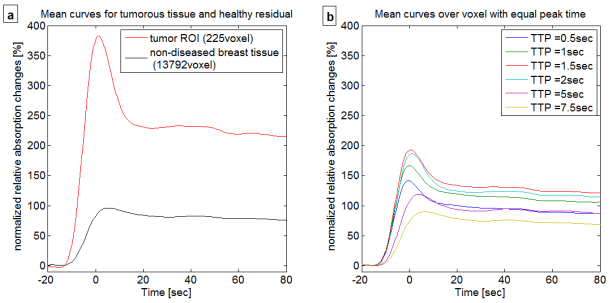

Figure 4. a) Volume-averaged ICG bolus signals for the tumor tissue (red) and healthy background tissue (black) for a representative case (33-mm IDC). b) Average curves for volumes with identical PA value.

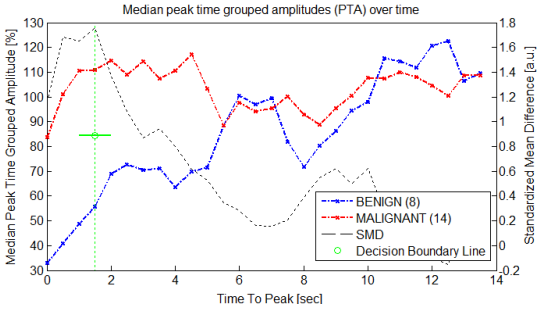

Figure 5. Peak time grouped amplitudes (PTA) vs. time for benign and malignant groups.

following t_0 computes the mean PA of all those voxels reaching their respective PA maximum at that time. This 'peak-time grouped amplitude' (PTA) parameter exhibits a significant difference when calculated for all benign and all malignant cases. As shown in Fig. 5 the difference is maximal shortly after the bolus arrival at t_0 + 1.5 s. After 6 s and up until 14 s the PTA is similar for both tissues. PTA(t_0 + 1.5 s) was computed for each subject and classified as 'malignant' or 'benign' according to a decision boundary, based on which a receiver-operator-curve-analysis was performed. A boundary of 84.4% yielded the best performance (sensitivity = 85.7%, specificity 87.5%).

4. Conclusions

Intrinsic and external contrasts in dynamic DOT can serve to evoke tissue-specific contrasts which are sensitive to the disease state of breast tissue. In both measurements, the malignant tissue shows a more compliant reaction to the provocation, as is expected from known vascular physiology. Several metrics have been defined which can serve to objectively judge the tissue's disease state.

While simpler to perform, the breathing maneuver proofed to be less amenable to the generation of reliable tissue characterization metrics than the ICG protocol. This is mainly caused by the inter-subject variation which can only partly be accounted for by the derived metrics. We conclude that a Valsalva maneuver may only be clinical useful if externally controlled (e.g., by monitored air stream and pressure) or if used in conjunction with a separate reference measurement (e.g., DOT measures from the contralateral breast [2]). It may be possible to improve the Valsalva results if subjected to a reader-independent classification scheme.

The measurement of transient ICG bolus dynamics in conjunction with a reader-independent metric has yielded very promising diagnostic performance. We plan the application of other classifications schemes and to expand the results of this limited retrospective study to a larger patient base and a prospective study.

5. Acknowledgements

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