Dynamic Angiothermography

A new technology for breast cancer screening and diagnosis

Prof. Gian Carlo Montruccoli

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BARD1: Dr. Irmgard Irminger
Dynamic Angiothermography (DATG)

- New functional diagnostic tool
- Based on the imaging of mammary gland’s normal vascularization and detection of its angiogenic micro-circulation
- Morphological, qualitative images of the breast’s functional blood supply
- Reproducible, non-invasive
- R&D with Dept Medical Physics, University of Bologna
- Clinical results for 7000 patients, 25-year Follow Up
- Excellent integration with other breast diagnostic techniques
Breast Cancer: Early Detection, Diagnosis, and Prognosis

**Imaging Technologies.**

NCI is funding research on a variety of technologies for breast imaging, including:

digital mammography,
elastography,
magnetic resonance imaging (MRI),
magnetic resonance spectroscopy,
ultrasound techniques, positron emission tomography (PET),
single photon emission computed tomography (SPECT),
thermography.

THREE FUNDAMENTAL CHARACTERISTICS OF DATG

• Each woman has her own strictly personal flowline pattern (like fingerprint)

• This pattern remains constant over decades in the absence of patho-physiological changes

• Pathological modifications are independent of tumor size and shape
Quantitative method
Based on the measurement of thermal gradients ($\Delta T$), evaluated by image coloration

Qualitative method
Based on the detailed patterns of functional blood flows
Experiments run at the University of Bologna’s Department of Physics tested the plate against the others on the market, especially as to spatial resolution (as high as a tenth of a millimeter) and response time. The results were excellent and the plate has now been patented in Europe and the United States.

From: “A new type of breast contact thermography plate: a preliminary and qualitative investigation of its potentiality on phantoms” - Physica Medica (Vol. XX, N. 1January-March 2004 pp.27-31)
University of Bologna’s Department of Physics

TEST 1

Spatial resolution (as high as a tenth of a millimeter)

Our plate

From: “A new type of breast contact thermography plate: a preliminary and qualitative investigation of its potentiality on phantoms” -
Physica Medica (Vol. XX, N. 1 January-March 2004 pp.27-31)
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Plate sensitivity

- We tried to reproduce blood flow lines in Dep. of Physics
- Insertion of the tube with warm water into the wax phantom
- Pointed terminations (normal flow lines)
Scheme of vascular anatomy of left breast

As vessels enter the breast, they get smaller and smaller, as they ramify.

Cutaneous projection of the breast’s main arteries.

When we put the DATG plate on the breast, it reveals normal vessels as end-pointed, because they are ramifying and their signature flowlines reach a vanishing point.
Normal angiothermographics flowlines reproduce the anatomy of the circulation of the breast.

- The flow-lines of each plexus should be centripetal, fade out as they terminate in their own area and be proportional to the contra lateral.
Upper internal quadrant of the left breast showing a marked anomalous flow line formed by countless vessels activated by a Lobular and Ductal Carcinoma in Situ with intraductal diffusion.
SUSPICIOUS FLOWLINES

• Deviations (all)
• Non-pointed terminations (all)
• Flowlines that go beyond their own territory
MALIGNANT FLOWLINES

• Two or more flowlines that cross one another: these are called malignant crosses or stars

• Flowlines that converge towards a central hotspot

• Flowlines that converge from different territories
Menopausal patient

«Malignant star»

Infiltrating Lobular Carcinoma

Biopsy zone

Mammography: no pathological findings

The lesion is between skin and muscle perpendicular to the end of the angiothermographic flow line.

Diagnosi:

Carcinoma lobulare multifocale classico infiltrante associato a focolai di carcinoma lobulare in situ.
• This 36-year-old patient, who said she was 8 weeks’ pregnant, can have the angiotest because it is harmless.
• The check-up showed a hot spot with flow lines from the acromial and the external mammary in the upper left external quadrant.
• An ultrasound was negative but the biopsy, performed under local anesthetics, returned LCIS as the histological result.
Progression of angiogenesis

Normal

Hyperplasia

In situ Cancer

Invasive cancer
Visualizing the angiogenic switch

Neovascularization in a rat tumor model

Images reproduced with permission from Dr Judah Folkman.
Immunohistochemical expression of VEGF-A and its ligands in non-neoplastic lesions of the breast sampling-assisted by dynamic angiothermography

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Abstract. The aim of this study was to investigate the expression of angiogenic markers, vascular endothelial growth factor A (VEGF-A) ligand and its receptors, VEGFR-1 and -2, in a series of biopsy-proven non-neoplastic lesions of the breast detected by dynamic angiothermography. We have also studied the vascular density demonstrated by CD31 immunoreactivity, in order to assess the potential of the imaging method to recognize lesions with an enhanced vascular network of clinical importance in routine breast examination. The lesions were classified as non-proliferative, proliferative without atypia and proliferative with atypia. VEGF was diffusely expressed in the epithelial cells of proliferative lesions in almost all cases. Similarly, VEGFR-1 and -2 also exhibited epithelial positive reactions in the majority of cases. VEGF-A and its receptors were also present in blood vessels. CD31 showed an increase in vascular proliferation at the periphery of proliferative epithelial lesions, but not in non-proliferative lesions. Our results, showing marked expression of VEGF by the epithelial proliferative lesions and neoangiogenesis at their periphery, confirm that these lesions can be detected by dynamic angiothermography.
**Histological findings**

- We performed 1,065 biopsies on 693 out of a total 7,003 patients from 1975 to 2006.

- Note first that the rate of epithelial lesions runs as high 70% if simple hyperplasia is considered. (Molecular tests showed a loss of heterozygosity in 90% of hyperplasia cases)

- Note too that pre-invasive lobular lesions were more than double the ductal, contrary to what is reported in literature. Why?

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>%</th>
<th>% Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>143</td>
<td>13.43</td>
<td></td>
</tr>
<tr>
<td>Mastitis and/or ectasia</td>
<td>184</td>
<td>17.28</td>
<td>30.71</td>
</tr>
<tr>
<td>Simple ductal hyperplasia</td>
<td>182</td>
<td>17.09</td>
<td></td>
</tr>
<tr>
<td>Florid ductal hyperplasia</td>
<td>243</td>
<td>22.82</td>
<td></td>
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<tr>
<td>Papillomatosis</td>
<td>48</td>
<td>4.51</td>
<td></td>
</tr>
<tr>
<td>Atypical duct hyperplasia</td>
<td>8</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Atypical lobular hyperplasia</td>
<td>23</td>
<td>2.16</td>
<td></td>
</tr>
<tr>
<td>Mixed atypical hyperplasia</td>
<td>13</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>16</td>
<td>1.50</td>
<td></td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>28</td>
<td>2.63</td>
<td></td>
</tr>
<tr>
<td>Mixed carcinoma in situ</td>
<td>15</td>
<td>1.41</td>
<td></td>
</tr>
<tr>
<td>Ductal microinvasive carcinoma</td>
<td>2</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Lobular microinvasive carcinoma</td>
<td>5</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Mixed invasive carcinoma</td>
<td>2</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Ductal invasive carcinoma</td>
<td>130</td>
<td>12.21</td>
<td></td>
</tr>
<tr>
<td>Lobular invasive carcinoma</td>
<td>16</td>
<td>1.50</td>
<td></td>
</tr>
<tr>
<td>Mixed invasive carcinoma</td>
<td>4</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Malignant phyllodes</td>
<td>3</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>1,065</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
One finding in particular indicates that in the normal state the duct’s microcirculation has a smaller surface area than the lobule’s and that the latter’s circulation is represented by sinusoids and is hence notably slower.

Comparison of Diagnostic Techniques
- 5913 Mammography 20-2-97
- 5913 left lateral 31-12-96
Pt 6128

Appearance of microcalcifications: LCIS 3 mm

MAMMOGRAPHY  LEFT 2-6-1998 MICROCALCIFICATIONS
Pt 6128

Appearance of microcalcifications: LCIS 3 mm

- MAMMOGRAPHY LEFT 2-6-1998
- Pz. 6128 Left Lateral Pre-op
Pt.6128 after surgery : Normal

- Pz.6128 Mammography 25-10-1999
- Pz.6128 lateral left 18-10-2000
A 40-year-old woman operated elsewhere for Ductal Infiltrating Carcinoma with radiotherapy. MRI shows a local relapse that is supported by DATG.
2° localization?
<table>
<thead>
<tr>
<th>ID</th>
<th>Age</th>
<th>RMN</th>
<th>DATG</th>
<th>X-MAMOGRAPHY</th>
<th>US</th>
<th>FAMILIARITY</th>
<th>HISTOLOGY</th>
<th>note</th>
</tr>
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<tbody>
<tr>
<td>BN</td>
<td>40</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>no</td>
<td>Infiltrating ductal carcinoma-relapse</td>
<td>Nipple discharge</td>
</tr>
<tr>
<td>SC</td>
<td>42</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>yes</td>
<td>Infiltrating Ductal Carcinoma</td>
<td>Pre-op chemotherapy</td>
</tr>
<tr>
<td>BB</td>
<td>30</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>no</td>
<td>Infiltrating Ductal Carcinoma 4 mm.</td>
<td>Mammary implants</td>
</tr>
<tr>
<td>DS</td>
<td>42</td>
<td>+/−</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>yes</td>
<td>Infiltrating lobular carcinoma-multicentric</td>
<td>Mammary implants</td>
</tr>
<tr>
<td>DPS</td>
<td>44</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>yes</td>
<td>Relapse following quartah</td>
<td></td>
</tr>
<tr>
<td>UP</td>
<td>55</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>no</td>
<td>2 cancer: -Infiltrating ductal (RMN and DATG) -ductal in situ only DATG</td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>45</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>yes</td>
<td>Ductal in situ 0.4 e 0.6 only with DATG</td>
<td></td>
</tr>
<tr>
<td>SM</td>
<td>60</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>no</td>
<td>Pre-invasive lesion</td>
<td></td>
</tr>
<tr>
<td>MC</td>
<td>49</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>no</td>
<td>Ductal in situ 0.4 e 0.6 only with DATG</td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>39</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>yes</td>
<td>Ductal in situ contralateral</td>
<td></td>
</tr>
</tbody>
</table>
DATG Applications
Detection of Breast Cancer
Tumore della mammella durante la gravidanza

- 6389 right lateral
- 23-6-2000
- 26th week of pregnancy

- 6389 right lateral
- 2-8-2000
- after biopsy
4779 after surgery: "Atypical lobular Hyperplasia"
Young Patient
17 year old: “papillary duct hyperplasia of the breast”
17 year old: “papillary duct hyperplasia of the breast”
post. op.
Monitoring the Therapy
Hormone Replacement Therapy
604 Long follow-up with HRT
Long follow-up with HRT and biopsy (Hyperplasia lobular and ductal)

With HRT

Without HRT

After surgery
Antiblastic Therapy
1661 After antiblastic therapy

- 1661  Left frontal 6-6-80
- 1661  Left frontal 19-6-80
1661 Monitoring antiblastic therapy

- 1661 Left XRM 29-5-80
  At diagnosis

- 1661 Left XRM 22-8-80
  After antiblastic therapy
2423 At diagnosis

- 2423 Left frontal 1-10-82
- 2423 Left lateral 1-10-82
2423 After 2 months of Tamoxifen

- 2423 Left frontal 2-12-82
- 2423 Left lateral 2-12-82
Benign: mastitis
(after 14 days of antibiotics)
Follow Up
MAMMELLA DESTRA: CARCINOMA CUTANEO INFIltRANTE G2 A MARGINI INFIltrATIVI (F) CON ESTENSIONE METASTATICA AD 1 LINFONODO INTRAMAMMARIO.
ANAPLASTICA NUCLEARE: MODERATA.
TESSUTO MAMMARIO CON MARCATA STEATINOCITOSI E REAZIONE GIANTOCITARE COME DA PRECEDENTE INTERVENTO.
METASTASI IN 2 LINFONODI DEL CAVO ASCELLARE SU 14 ESAMINATI.

MAMMELLA SINISTRA: TESSUTO MAMMARIO CON ASPETTI DI INVOLUZIONE DEI LOBULI E DI FIBROSI STROMALE.

RECETTORI ESTRUSCOLARI: 80-120 bassa espressione; >20 alta espressione.
RECETTORI PROGESTATIVI: 80-120 bassa espressione; >60 alta espressione.
INDICE DI PROLIFERAZIONE CON ANTICORPO XF 81.5/(<5 bassa proliferazione; 5-10 moderata proliferazione; >10 alta proliferazione).

ERG: NEGATIVO.

GRIGIONI PROF. WALTER FRANCO
Integrated Diagnosis
A: Ductal Infiltrating Carcinoma G3

B: Ductal Infiltrating Carcinoma with intraductal G2

Patient with fine needle aspiration (elsewhere) positive for infiltrating ductal carcinoma. A

The DATG shows a second neoplastic localization B

34 year old patient
Hormonal stimulation for infertility

Controlateral is normal

3N+/15
Other Applications
4786 melanoma

- 4786 clinica 10-3-91
- 4786 laterale destra 10-3-91
4786 melanoma

- 4786 laterale destra 10-3-91
- 4786 laterale sinistra 10-3-91
Screening
DATG pattern remains the same over 16 years (in absence of pathology)

- 1041 15-3-79
- 1041 9-11-95

DATG is useful for screening
DATG pattern remains the same over 20 years (in absence of pathology)

DATG is useful for screening
DATG pattern remains the same over 25 years (in absence of pathology)

DATG is useful for screening

- 657 14-3-78
- 657 27-11-03
DATG pattern changes in presence of pathology

The two flow-lines (white arrow) of the external mammary are initially normal.

15 months later one remains the same and the other disappears to form a new line with the acromial (red arrow). Both go on to feed a lobular in situ carcinoma (1 mm in diameter).

This new flowlines (12-15 cm long) feed such very small tumor.

1° Visit : normal

2° Visit : suspect
Dramatic change: Mixed lobular/duct CIS
Dynamic angiothermography
A new technology for breast cancer screening and diagnosis

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F.I.G.O. Oncological Committee
S.I.S. Expert Member

Thank You