Training Course in Sexual and Reproductive Health Research
Geneva, February 2009

Dynamic Angiothermography
A new technology for breast cancer screening and diagnosis

Prof. Gian Carlo Montruccoli

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Geneva Foundation for Medical Education and Research
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 vs. QUALITATIVE

Old Contact Thermography
- Quantitative method
- Based on the measurement of thermal gradients ($\Delta T$), evaluated by image coloration

Dynamic Angiothermography - DATG
- 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. 1 January-March 2004 pp.27-31)
TEST 1

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

Our plate

Commercial 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)
University of Bologna’s Department of Physics

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)
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)

Plate sensitivity
Scheme of vascular anatomy of left breast

Cutaneous projection of the breast’s main arteries.

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

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
- In situ Cancer
- Hyperplasia
- Invasive cancer

DATG
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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Received May 8, 2007; Accepted June 27, 2007
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>
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<tr>
<td>Florid ductal hyperplasia</td>
<td>243</td>
<td>22.82</td>
<td>39.91</td>
</tr>
<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>4.13</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>5.54</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>0.85</td>
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<tr>
<td>Mixed invasive carcinoma</td>
<td>2</td>
<td>0.19</td>
<td></td>
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<tr>
<td>Ductal invasive carcinoma</td>
<td>130</td>
<td>12.21</td>
<td></td>
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<tr>
<td>Lobular invasive carcinoma</td>
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<td>1.50</td>
<td>14.09</td>
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<tr>
<td>Mixed invasive carcinoma</td>
<td>4</td>
<td>0.38</td>
<td></td>
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<tr>
<td>Malignant phyllodes</td>
<td>3</td>
<td>0.28</td>
<td>0.28</td>
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<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.
False Positive 10%-15%
False Negative 4 cases (1,065 biopsies)

TO BE CONFIRMED WITH A PROSPECTIVE STUDY
Screening or prevention?

18 years earlier…
- DATG: 19-3-96
- X-Ray Mammography: 15-3-96
After surgery
Comparison of Diagnostic Techniques
Pt 6128
Appearance of microcalcifications: LCIS 3 mm.
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
<table>
<thead>
<tr>
<th>GROUP A</th>
<th>No. of cases</th>
<th>Age (years)</th>
<th>Size</th>
<th>Rx</th>
<th>DATG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Min</td>
<td>Max</td>
<td>Mean±SD</td>
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<tr>
<td>ALH</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>ADH</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>35</td>
<td>58</td>
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<tr>
<td>MAH</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>16</td>
<td>66</td>
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<tr>
<td>LCIS</td>
<td>10</td>
<td>2</td>
<td>8</td>
<td>41</td>
<td>72</td>
</tr>
<tr>
<td>DCIS</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>45</td>
<td>51</td>
</tr>
<tr>
<td>MCIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMC</td>
<td>1</td>
<td>1</td>
<td></td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>DMC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMC</td>
<td>1</td>
<td>1</td>
<td></td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>LIC</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>40</td>
<td>74</td>
</tr>
<tr>
<td>DIC</td>
<td>67</td>
<td>34</td>
<td>33</td>
<td>31</td>
<td>81</td>
</tr>
<tr>
<td>MIC</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>103</td>
<td>48</td>
<td>55</td>
<td>16</td>
<td>81</td>
</tr>
</tbody>
</table>

Legenda:
ALH (atypical lobular hyperplasia) - ADH (atypical ductal hyperplasia) - MAH (mixed atypical hyperplasia)
LCIS (lobular in situ cancer) - DCIS (ductal in situ cancer) - MCIS (mixed in situ cancer)
LMC (lobular microinvasive cancer) - DMC (ductal microinvasive cancer) - MMC (mixed microinvasive cancer)
LIC (lobular invasive cancer) - DIC (ductal invasive cancer) - MIC (mixed invasive cancer)

Table 2. Overall diagnostic results by means of DATG together with RX Biopsy at first visit (group A)
<table>
<thead>
<tr>
<th>GROUP B</th>
<th>No. of cases</th>
<th>No. of cases</th>
<th>Age (years)</th>
<th>Size</th>
<th>Rx</th>
<th>DATG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Min</td>
<td>Max</td>
<td>Mean±SD</td>
<td>Min</td>
</tr>
<tr>
<td>ALH</td>
<td>4</td>
<td>4</td>
<td>38</td>
<td>56</td>
<td>46.7±7.4</td>
<td>4</td>
</tr>
<tr>
<td>ADH</td>
<td>1</td>
<td>1</td>
<td>45</td>
<td>45</td>
<td>45.0</td>
<td>4</td>
</tr>
<tr>
<td>MAH</td>
<td>5</td>
<td>1</td>
<td>47</td>
<td>83</td>
<td>62.0±13.7</td>
<td>5</td>
</tr>
<tr>
<td>LCIS</td>
<td>6</td>
<td>2</td>
<td>37</td>
<td>53</td>
<td>43.5±5.9</td>
<td>5</td>
</tr>
<tr>
<td>DCIS</td>
<td>2</td>
<td>2</td>
<td>51</td>
<td>65</td>
<td>58.0±9.9</td>
<td>5</td>
</tr>
<tr>
<td>MCIS</td>
<td>5</td>
<td>2</td>
<td>48</td>
<td>74</td>
<td>58.8±16.6</td>
<td>4</td>
</tr>
<tr>
<td>LMC</td>
<td>2</td>
<td>1</td>
<td>37</td>
<td>44</td>
<td>40.5±4.9</td>
<td>2</td>
</tr>
<tr>
<td>DMC</td>
<td>1</td>
<td>1</td>
<td>51</td>
<td>51</td>
<td>51.0</td>
<td></td>
</tr>
<tr>
<td>MMC</td>
<td>3</td>
<td>3</td>
<td>42</td>
<td>62</td>
<td>50.7±10.3</td>
<td>6</td>
</tr>
<tr>
<td>LIC</td>
<td>8</td>
<td>3</td>
<td>45</td>
<td>77</td>
<td>56.6±10.1</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>14</td>
<td>23</td>
<td>83</td>
<td>52.7±11.1</td>
<td>4</td>
</tr>
</tbody>
</table>

Legenda:
ALH (atypical lobular hyperplasia), ADH (atypical ductal hyperplasia), MAH (mixed atypical hyperplasia), LCIS (lobular in situ cancer), DCIS (ductal in situ cancer), MCIS (mixed in situ cancer), LMC (lobular microinvasive cancer), DMC (ductal microinvasive cancer), MMC (mixed microinvasive cancer), LIC (lobular invasive cancer), DIC (ductal invasive cancer), MIC (mixed invasive cancer)

Table 3. Overall diagnostic results by means of DATG together with RX Biopsy during follow-up (group B)
2° localization?
DATG Applications
Detection of Breast Cancer
Breast tumor during pregnancy

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

- 6389 right lateral
  2-8-2000
- after biopsy
Genetics
4779 after surgery: “Atypical lobular Hyperplasia”
Breast Cancer Familiarity: close follow-up
Appearance of disease
Young Patient
17 year old: “papillary duct hyperplasia of the breast”
17 year old: “papillary duct hyperplasia of the breast” post-op.

3634-front left  23-6-87
Pre-op.

3634-front left  2-12-02
Post-op.
Monitoring the 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
A 54-year-old woman.

The external upper quadrant of the right breast shows an incomplete malignant ring composed of numerous short flowlines of external mammary, acromial and internal mammary origin, all ending in spatula terminations.

3583 Right lateral 21-4-87
After 2 cycles of preoperative chemotherapy, the DATG pattern has become negative. All the abnormal flowlines have largely disappeared.

The subsequent biopsy revealed a 1 cm invasive ductal carcinoma.
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
After 2 months of Tamoxifen
Benign: mastitis
(after 14 days of antibiotics)
Integrated Diagnosis
34 year old patient
Hormonal stimulation for infertility

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

Controlateral is normal

3N+/15
Other Interesting Cases
2125 von Recklinghausen’s disease
2125 von Recklinghausen’s disease

- 2125 Left lateral
- 2125 Left lateral
4797
Angioma without heat transmission

4797  Left: angioma 21-3-91

4797 Left lateral 21-3-91
Herpes zoster

3786 Left frontal 1-3-88

3786 Left frontal 1-3-88
DATG “cool”
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
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.
Dramatic change: Mixed lobular/duct CIS
NEXT STEP

- Double-blind prospective study comparing DATG, US, X-Ray and MRI.
- Sensitivity & specificity of DATG / X-Ray against Histology as "gold standard".
- DATG sensitivity to young BRCA 1&2 carriers.

International clinical protocol coordinated by Geneva Foundation for Medical Education and Research & World Health Organization (WHO). Department of Reproductive Health and Research.
Dynamic angiothermography
A new technology for breast cancer screening and diagnosis

Prof. Gian Carlo Montruccoli
Gynaecologist, member of the Gynaecology and Oncology Committee of the International Federation of Gynaecology and Obstetrics (FIGO)
Member of the International Society of Senology (S.I.S.) Committee of Experts

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EQUIPMENT
Benign microcalcification

Comparison with the other technique

The entire history of the patient

CAD – Computer Aided Diagnosis

Malignant microcalcification

Comparison with the other technique

The entire history of the patient
FDA approved Breast Thermography in 1982

Bio-morphological events in the development of the human female mammary gland from fetal age to puberty.


Definition of the microvascular pattern of the normal human adult mammary gland.


G.C. Montruccoli, D. Montruccoli Salmi, F. Casali

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

Daniele Montruccoli, Franco Casali, Stefano Brusori, Paolo Barillari, Corrado Scipioni et Gian Carlo Montruccoli

“L’angiothermographie dynamique : un avenir ?”
L’AGENDA GYNECOLOGIE, Mars 2005 pag.42-43

G.C. Montruccoli, D. Montruccoli, D. Barnabe’, V. Altimare

Thermography fiction or reality?
INTERNATIONAL JOURNAL OF OBSTETRICS AND GYNAECOLOGY Vol. 83 Supplement N.3 pag.18 November 2-7 2003


Clinical application of a new thermographic plate: histophathological findings of 1027 breast lesions.

95TH AMERICAN ASSOCIATION FOR CANCER RESEARCH
AACR ANNUAL MEETING 27-31 MARCH 2004


Angiogenesis and VEGF expression in pre-invasive lesions of human breast.

JOURNAL OF PATHOLOGY 2004; 204: 140-146
Practical Considerations

- **DATG** is:
  - *Rapid*
  - *Economical*: (limited equipment and maintenance costs)
  - *Completely non-invasive*

- Can be used *at any age*

- *Very good compliance*

- *Breast cancer prevention (even detection of lobular neoplasia)*

- No radiations, No chemical, No pain

- Repetitive and Reproducible

- Rapid performance time, immediate response

[Email: daniele@montruccoli.it]
Prof. Gian Carlo Montruccoli

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

Thank You