Dynamic angiothermography
A new technology for breast cancer screening and diagnosis

Giancarlo Montruccoli, Daniele Montruccoli

Physicians everywhere often find themselves in doubt, whence their desire to check their opinions and decisions further. This usually occurs in senology for two kinds of reasons or in two situations - one of human cast and the other purely technical. As we all know, the human side of the equation is the real terror women have when spectre of breast cancer is raised. They need to be reassured immediately since they may think of a tumour even for the smallest of discomforts. So, we as physicians know that being good and providing the best care coincide when we can deliver not only a negative response for the tumour but an immediate one as well. Yet the need for a quick decision very often runs into a number of technical, bureaucratic, economic and other hurdles that can wither the good intentions of any doctor and well organised facility. The latter or technical side is, perhaps, somewhat more important and harder to solve. It derives, I think, from the fact that the two main diagnostic techniques we have today, mammography and ultrasound are based on the study of desmoplasia, that is, on the host’s connective reaction to the tumour. Yet desmoplasia varies even in the same patient depending upon age and differs depending on the histological type of tumour.

Such a broad range of individual reactions greatly constrains diagnostic precision and is the source of many doubts. There is too the fact that neither of these techniques is predictive, so that we must wait for the host’s reaction to an already existing tumour, even the smallest one, before a diagnosis is possible. The 10-15% of what we called ‘intercurrent’ tumours that show up during screening can be ascribed to the impossibility of these two techniques in predicting tumours, but certainly not to the poor quality of the instruments used or a lack of technical skills. In other words, no matter how much upgrading radiological and ultrasound machines may be heir to, the results they deliver will always be subject to the biological factors of desmoplasia. Indeed, if we recall the human side of the equation, the two sides merge here in that a certain dualism emerges over time is there or isn’t there a tumour?

Thus, practically speaking, there do not appear to be other possibilities today, no other diagnostic shades of meaning or differences, that can provide a more accurate tool in helping our patients. With colon cancer, for example, there is a normal situation, a polyp that can turn into a tumour. But not in senology, where we go from nothing to cancer. Let me apologise if I seem too polemical or aggressive, or perhaps even mistaken. I am not in the least suggesting that current diagnostic techniques are more or less seriously flawed, or to ignore the enormous amount of work that these
tools have helped us accomplish so far and will continue to do. Indeed, I have taken the liberty to point out the drawbacks of these two methods because I use both in my clinical work every day. If anything, my intention was rather to highlight the need to integrate their use with other approaches, such as DATG (Dynamic Angiothermography), M.R.I., P.E.T. or any others that may be developed in future. In effect, it is my conviction that our machines are quite valid and have achieved a high level of perfection.

What we must do, therefore, is change our strategy. We must manage to pinpoint a tumour before his birth, without waiting for telltale symptoms of onset to show up as we now do with mammography and ultrasound. One novel strategy might be to look for *in vivo* signs of tumour angiogenesis, which always accompanies pre-invasive states and *in situ* carcinoma. Pinpointing an angiogenetic event thus corresponds to locating an epithelial lesion for biopsy. This is in fact the main purpose for which Dynamic Angiothermography, as my method is called, was designed. So, let’s take a brief look at the scientific and clinical bases for the link between neo-angiogenesis and pre-invasive breast lesions.

One good approached seemed to be thermography, which markedly differs from the other techniques. Yet for a number of reasons it was called into question, above all I think because there was a certain confusion about interpreting the data. For example, right form the start it was attempted to quantify the (delta) $\delta$-T responses of the thermograph sheets against those of contact thermography. By contrast, Dynamic Angiothermography is not really thermography in that, to begin with, it requires a cooling of the skin during the test so as to get a good quality image.
While there are still very few reports in the scientific literature in this connection, they are quite telling.

Along with Prof. Bevilacqua and his co-workers, we have a paper in press on the mammary gland’s microcirculation. 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.

The capillary micro-circulation around the ducts and lobules have different traits in the sense that the lobular circulation is marked, and above all, formed by numerous sinusoids slowing the supply. This is probably due to the fact that the lobule represents a functional unit of the gland, with its terminal duct-lobular unit. We can see on the one hand the anatomical representation of the duct and lobule circulation and on the other its computer generated image for a clearer view.
Here we have an immuno-reactive malignant cell at VEGF
and two cases of immuno-reactivity at CD34 for neo-angiogenesis in two cases of in situ ductal carcinoma.

This study of 120 cases of the usual type of hyperplasia, atypical ductal and lobular hyperplasia, well, intermediate and poorly differentiated intraductal carcinoma and lobular in situ carcinoma shows that an increase in blood supply is necessary for the appearance of any type of epithelial proliferation. Both typical and atypical hyperplasia have the same higher value of vascular density and would bear a higher risk of progression.

The same study compared vascular density around the lesion to that of the same anatomical structures close to a millimetre but normal. THIS IS WHY WE ARE INCLINED TO THINK THAT NEO-ANGIOGENESIS is required when promotion takes place.

We can thus note that vascular density progressively increases along with the importance of the lesions.
This technique is based on a new diagnostic plate tested at the University of Bologna’s Department of Physics.

Several 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

several experiment run at the university of bologna, department of physic tested the plate against the other on the market, especially as to spatial resolution (as high as a tenth of a millimetre ) and response time. The results were excellent.
**TEST 1**

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

**Our plate**

**Commercial plate**

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**Spatial resolution**

**TEST 2A after 3’’**

response time

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After only three seconds the image appears
A small tube with coloured water is inserted in another wax phantom. The plate is sensitive enough to pick up the drop in heat, accurately registered, at the insertion point.

This shows by comparison that the plate can pick up the heat from one of two veins spaced only 1-cm apart. And at the same distance from the skin. The amount of blood flow in that vein is evidently greater.
Achieving this kind of functional blood flow study requires a very sensitive tool, with fine spatial resolution, that can keep the image stable for accurate reading, evaluation and recording.

To better understand the scientific basis of this diagnostic technique we had to describe the normal vascularization of the breast and the blood supply respect the DATG analysis.

The anathomical circulation is divided into different, while homonymous, territories respect to DATG analysis.

Inside each territory Angiothermography detects a localized circulation.
Let’s talk a bit here about semeiotics so as to better understand what the points we are illustrating. There are normal, benign suspect and malign flow lines. The normal lines always reproduce the anatomical circulation in the various areas and terminate towards the nipple in pointed ends. By contrast, suspect and malign lines are found outside the normal supply flow.

Acromial Territory
Normal Flow-line

Abnormal Flowlines
The flowline evidenced clearly show nothing functionally and anathomically coherent
Left breast, front view. The branching of the internal mammary normally run towards the nipple, gradually becoming thinner until disappearing. Here, instead, we see the exact opposite: they start off thin, turn upwards and end up swollen (mixed lobular-ductal, micro-invasive cancer).

The flow is functional in that it was not possible to form a single blood vessel of such a strange and coarsely cast shape. Rather, it took shape using a countless number of anatomically anastomosed capillaries and very small vessels (in this case from the internal mammary and acromial areas) that are feeding the lesion. It’s surprising that an epithelial pathology 2-3-mm in diameter can trigger an overall blood flow whose diameter is equal to or greater than an artery’s. This in all likelihood is because the capillaries involved are so numerous, densely packed and functionally aligned towards the lesion as to simulate an arterial pathway. These capillaries are probably flanked by others supplying their circulation but as the latter are increasingly more scattered and less numerous the plate does not pick them up.

Cutaneous projection of the breast’s main arteries

The flow-line of each plexus should be centripetal, fade out as they terminate in their own area and be proportional to the contralateral.
A 45-year-old woman. The DATG pattern of the left breast contains irregular flowlines, including a slight deviation and a spatula termination. Appropriate air-cooling of the breast further clarified the captation phenomenon (c). Histological examination revealed a mixed duct/lobular microinvasive carcinoma.

As we have noted, dynamic angiothermography is based on a qualitative, rather than quantitative, evaluation. To get good quality, readily interpretable images, the skin must be cooled so as to erase any overlying, basic heat. Here is an example: while the first image is already visible but not well-defined, with cooling we can now clearly see that two flow lines, which are abnormal as to both termination and pathway, run from the external and acromial mammary and refer to a micro-invasive mixed carcinoma.

THREE FUNDAMENTAL CHARACTERISTICS OF DATG

- Each woman has her own strictly personal flowline pattern
- This personal pattern remains constant over decades in the absence of pathophysiological changes
- Pathological modifications are independent of tumor size and shape
We shall have ample opportunity over the coming days to see the various ways DATG can be employed and to work up together protocols for its use. Today, let me briefly illustrate how many years of effort led to ever greater understanding of the unit’s real potential and, especially, how to accurately read, on a case-by-case basis, the meaning of the patterns shown and their reproducibility.

*DATG pattern remain the same along 25 years in absence of pathology*

*The reproducibility of the technique permit a long follow up without changes of the pattern. So DATG is useful for screening*

So, as we can see, this approach provides a very broad range for diagnostic investigation once we understand how it works. And that is in fact very easy to explain. Simply put, DATG studies the breast’s functional blood supply. The blood flow is part and parcel of every pathophysiological event of the body, and in the breast we can see and understand what it’s doing because the breast is an external organ of the body and its blood flow is immediately beneath the skin.

That’s why we can see it:
• 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 flowline (12-15 cm. long) feed such very small tumor.

Then, too, all the anatomical areas of blood supply contribute notably to the demands of a tumour.
Malignant Flowline

two or more flowlines that cross one another

flowsline that converge from different territories

flowsline that converge towards a central hotspot
One of the features of cancer is what can be called ‘captation’ or commandeering, that is, when two or more flow lines run towards an ideal point where the tumour is located. This image clearly shows the blood-flow commandeering by a lesion.

In these cases, angiogenesis, which combined with the normal circulation, was also present. In others cases where it was not found, there was only a normal dilation of existing blood vessels for the momentary needs of an event (mastitis): here we can see the dilation disappearing because the abscess has healed and blood flow is returning to normal.

Clinical and angiothermographic representation of acute mastitis.

Acute mastitis is always a source of marked anxiety, especially when it occurs after breast feeding and after the age of 40 since it may be associated with cancer. Here, the initial DATG pattern can overlap with that for an inflamed carcinoma with malign oedema: the external right mammary has three flow lines running towards a supra-areola hot spot, with one line exhibiting an irregular termination, i.e. not pointed at the end. The nipple appears hot. A fifteen-day regime of antibiotics was enough to get a clear diagnosis based on the marked change in the DATG image showing an altogether normal picture.

Demonstration of the functional nature of DATG pattern, initial pregnancy
Left breast, front view. The patient came in for a routine check-up on 12 September, one month after an initial examination, which proved negative, for a sharp pre-menstrual mastalgia that had scared her because it was altogether unusual. Here we see the DATG pattern of the left breast, front view, on 12 September and on 15 October. We can see the flow lines have grown notably in blood supply capacity. A positive gonadotropin test and the patient’s medical history confirmed the onset of pregnancy 7-10 days prior to the second DATG test - a clear demonstration of the functional nature of DATG’s patterns.
A 25-years old woman beginning to take Oral Contraceptives which elicits a pattern like pregnancy’s with suspension, the image returns to normal.

A 16-month-old patient, initial visit.
A swelling round the nipples suggests telarche. Note on both sides of the DATG image the two hot spots related to several flow lines. Given her young age and the fact that the clinical and laboratory test results were negative, the patient entered follow-up: after a mere 8 months the overall picture is negative. We thin it was caused by over-stimulation from foods containing estrogens.

This slide shows that the blood flows diminish in menopause.

There can thus be an approach that exploits an overall strategy to provide continuous and organised care throughout a patient’s life.

Histological findings
Results

Our results derive from 1,027 biopsies run on 591 patients (including counter-laterals and those performed subsequently on the same patient) up to 2001. We are also trying to recover the records of the mammographies not taken at our facility so as to come up with an accurate measure of sensitivity and specificity with respect to mammography. These data are in effect the result of a retrospective study. Yet they immediately make clear that a notable rate of detected pathology concerns so-called pre-invasive or pre-cancerous epithelial lesions.

Table: Results of 1,027 biopsies according to age.

<table>
<thead>
<tr>
<th>No. of women</th>
<th>&lt;=39 yrs</th>
<th>40-49 yrs</th>
<th>&gt;49 yrs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of biopsies</td>
<td>212</td>
<td>420</td>
<td>395</td>
<td>1,027</td>
</tr>
<tr>
<td>Negative</td>
<td>129 (60.8%)</td>
<td>182 (43.3%)</td>
<td>181 (45.8%)</td>
<td>492 (47.9%)</td>
</tr>
<tr>
<td>Pre-cancerous</td>
<td>57 (26.9%)</td>
<td>169 (40.2%)</td>
<td>98 (24.8%)</td>
<td>324 (31.5%)</td>
</tr>
<tr>
<td>Pre-invasive</td>
<td>8 (3.8%)</td>
<td>23 (5.5%)</td>
<td>27 (6.8%)</td>
<td>58 (5.6%)</td>
</tr>
<tr>
<td>Invasive</td>
<td>18 (8.5%)</td>
<td>46 (11.0%)</td>
<td>89 (22.5%)</td>
<td>153 (14.9%)</td>
</tr>
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This is what characterises DATG’s diagnostic activity, which is based above all on the study of tumour angiogenesis. Even the very young average age at which the biopsies were performed is due both to the capability of using this approach with women of all ages and to the fact that angiogenesis is a phenomenon of such earliness as to precede the onset of the tumour itself.

While DATG may be a useful diagnostic tool, I have always been mindful of the fact that with science in general and medicine in particular absolute certainty does not exist. As noted before, I use all three techniques together mammography, ultrasound, DATG in my surgery so as to arrive at the most accurate diagnosis possible, what I call an integrated diagnosis. In other words, rather than planning a patient follow-up regime according to a specific timetable or target dates, as for example with screening, I prefer to tailor check-ups and use the various diagnostic methods on the basis not only of clinical data or symptoms but also on age and family history of cancer. In this approach, one looks to corroborate the DATG diagnosis mainly via ultrasound, especially for young women. If the DATG pattern has remain unchanged over two years, I think it is useless to schedule another mammography merely to keep to a protocol drawn up with other criteria. Indeed, the patient can have a DATG check-up every 6-8 months and the follow-up mammography can be postponed for a year or two.

In effect, it has been my experience to assess a suspect response from mammography with DATG to decide whether or not a biopsy is called for. Simply put, the idea here is to deploy the most useful features of each diagnostic tool to the case at hand. So, If there is a doubt about an in situ carcinoma, we look for micro-calcifications with mammography, and if there is a nodule, try to determine is it’s solid or liquid using ultrasound, all the time checking how much blood is flowing to the given area. In my experience, this approach elicits a notable reassurance in the patient, who is encouraged to continue in the follow-up regime. Indeed, after a certain monitoring period, the patient worries much less if a biopsy is needed, accepting it more readily because she knows that it merely has to do with a small lesion.

A great many of my patients have been in follow-up for more than 25 years. Indeed, it’s thanks to DATG that this kind of monitoring regime can be implemented, which has the added advantage of rapid response to the small breast problems that arise suddenly and that arouse so much anxiety in our patients.

I am very well aware that what I’m saying is the fruit of gradual developments over many years and cannot be transplanted all at once into public health programmes for a number of organisational reasons. Yet it is my conviction that public health is precisely the arena in which this approach has
its best application because its manifold range of diagnostic potential can readily be divided into the fields of observation and patient care.

While we shall have time in the days to come to discuss all the initiatives that can be developed by integrating mammography and ultrasound techniques with DATG, a brief outline seems to be in order here. Let’s focus for the moment then on just two of these very salient issues: Hormone Replacement Therapy (HRT) and BRCA 1 and 2 carriers. We are all familiar with the ongoing debates, which often turn into scientific papers on the drawbacks or advantages of HRT as a causal factor in breast cancer. While the advocates of one or the other thesis are more or less numerically equal, the number of worried patients who do not know what to do is growing day by day, at least in Europe.

It seems to me that the reason for these conflicting responses resides chiefly in the fact that they result from study designs that are far too different from one another. If we take, for example, the data after five years of treatment for a disease like breast cancer whose sub-clinical course can run as long as 15 years, it becomes evident that the results can be contrasting, if not altogether contradictory. With an instrument like DATG, however, patient monitoring becomes personalised, rather than merely statistical. It is my conviction that many women reach peri or menopausal age with pre-invasive epithelial lesions that cannot always be diagnosed with the usual techniques and that for biological reasons have not progressed to cancer. It is precisely during the time when these lesions should be on the way towards apoptosis because the monthly stimulus is lacking that the stimulus of HRT kicks in, triggering in some cases their progression. The problem may thus be not so much a matter of dose, type or duration of HRT as a matter of determining which patients can and which cannot undergo such treatment. As we have seen, DATG can both localise pre-invasive lesions and detect functional changes in the blood supply during follow-up in relation to the appearance of these lesions.

Let’s look at two examples.
A patient who began check-ups at 42 years old. For clarity’s sake, let’s take the image of the external left mammary area, which is normal on all counts. Over the years the pattern remains just about the same until, at 52, it tends to disappear with the onset of menopause. She then begins HRT, but as of the latest check-up this DATG pattern has not changed.

This 49-year-old patient has an anomalous flow line in the lower right internal quadrant traceable to the internal mammary area. This flow line has been deviated, has an abnormal termination and
is altogether disproportionate to her age. It is accompanies by another flow line that runs almost parallel to the former, as if being commandeered. The overall picture thus shows an altogether unjustified blood supply with respect to the case’s clinical profile. She is advised to suspend HRT, which she had started a year earlier.

Even stopping HRT did not elicit any notable signs of improvement during follow-up (which lasted to September 1997), and a biopsy was scheduled. The histological response was atypical ductal-lobular hyperplasia. After surgery, the patient resumed HRT and her follow-up shows that the anomalous flow lines have disappeared.

This may be taken as a good instance of public health care for women who opt for HRT and can make that decision more calmly than is possible today. The second case, in which DATG would be very useful because of its performance specifications, is as much of public interest as it is a matter that comes under the domain of hospitals and universities in that it involves the carriers of the BRCA 1 and 2 genes. As we all know, the only treatment on offer today in the United States and Europe is prophylactic mastectomy. Indeed, it is a particularly difficult decision to make as the incidence of cancer in these women is not even 60%. DATG can be very useful here.

The first reason why these patients have such a difficult time dealing with their situation as carriers of cancer-related genes is that this kind of tumour strikes them at an early age, that is, when mammography cannot monitor them with assurance. Another reason is that their cancer arises in a hurry, so to speak, and hence does not fit in well with screening protocols. Yet the main reason is the usual one it is not predictable by mammography and so these patients have no clinical way of even assessing what their probabilities are of being stricken or not in future. Whence their painful decision to opt for surgery to prevent cancer.

By way of explaining just how useful DATG can be here, let me show you this case.
The patient had her first examination at 24 because she is a BRCA1 carrier. She has an anomaly in the upper left quadrant of the external mammary. Given her youth, it is decided to rule out a biopsy and monitor her closely in follow-up. The pattern is unchanged 6 months later; a biopsy is performed and returns an in situ lobular carcinoma. At the post-op check-up, the image has completely returned to normal.
Her status today is a picture of perfect health, there are no suspect signs, and she can conceive without worry. She is keeping to her follow-up, and I think that DATG will let us know if any epithelial lesions appear in future.

There is not to my knowledge a diagnostic technique for the breast that is more innocuous than this - all that’s needed to run it is simply to place a thin sheet of air-cooled plastic on the breast. DATG is non-invasive, does not require a contrast medium and can be repeated as often as desired. Its run time is very fast: the entire visit, which is called the ‘angio-test’ and includes taking the patient’s history and a clinical examination, usually takes no longer than 15 minutes. This rapid visit time, which also makes possible a high number of angio-tests per working day, is matched by the immediate response, another big advantage. Indeed, it is an advantage both for the attending physician, who can advise the patient about any developments, and for the patient herself, who is immediately informed of the situation without having to wait days filled with anxiety for a response. All of this greatly enhances patient compliance with DATG.

Note, too, that the potential uses of DATG really increase when we realise its diagnostic capability is the same at any and all ages. This is a notably practical and useful feature in clinical work because it enables us, as attending physicians, to provide unlimited care for patients with breast problems. Although ultrasound can be useful on many an occasion with young women, it is not as useful as DATG in my experience, while combining the two approaches enhances overall usefulness a great deal.
It might be argued that increasing the number of patients increases costs. While this is true if we look at screening, it may not be so if we can schedule our patients according to proper organisational criteria and protocols. In my own experience, for example, I have had to operate on many patients two or three times because their biopsies showed pre-invasive lesions (even the same patient 2 or 3 times with the same histological result) - patients that are still in follow-up and have not developed cancer. I realise of course that such examples imply a perfect world but, let me add, they invite us at least to take up the challenge. If we can achieve even some degree of organ-specific prevention with DATG, we really should revise the way we calculate our figures.

We are not very adept at taking into account the state of anxiety of very young women, in part because cancer strikes this age group less frequently and in part because we do not include them in screenings. Yet, even without noting that the average age for this disease is getting younger, I firmly believe that many lives can be saved if diagnosis starts a few years earlier.

Let me at this point share a few personal views with you. As a disease, breast cancer is marked by several traits that at times have not been fully appreciated.

The first is a sub-clinical period that usually lasts many years.
This patient was 32 at her initial check-up. The right breast shows a low line running from perforant posterior to the external upper quadrant and ends in a kind of commandeering. Mammography and ultrasound were negative and no biopsy was performed for ethical reasons and because I was unable to interpret the flow line. This pattern held through years of subsequent check-ups, thereby seeming to provide full reassurance because it remained unchanged and because the series of later mammographs always returned a negative response. After 18 years in follow-up and 2 years after the last negative mammograph, malignant micro-calcifications appeared corresponding to a 7-mm invasive ductal cancer. This case shows on the one hand how long the sub-clinical period can be (Liotta has noted a period of 15 years in a recent paper) and on the other how I too can make a mistake.

The second is that this disease is notably dependent on a patient’s response, especially when it comes to hormonal therapies. The third is that, while the mortality rate has in part been lowered, the incidence of breast cancer has not despite all the efforts of the worldwide scientific community, health-care workers and social services.

These are the clinical factors of breast cancer that we must bring under control insofar as is humanly possible. Indeed, they have come to the fore again and again in my long experience with DATG. This is an instrument that we can use to lower the sub-clinical time it takes to get a diagnosis, it can help us to control the effects of hormonal therapies, and it can show us where pre-
invasive lesions are. What is certain is that with it we can at least save our patients some degree of anxiety and pain.