Biomagnetism in gynaecologic oncology. Our experience in Greece

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Summary

Our experience in the application of biomagnetism in gynaecologic oncology is presented. We provide a brief description of our research work in the investigation of biomagnetic activity in benign and malignant ovarian and breast diseases, and an evaluation of uterine myomas, providing a new approach of biomagnetism as a non invasive imaging modality for assessing gynaecologic tumours.

Key words: SQUID; Benign breast lesions; Malignant breast lesions; Benign ovarian lesions; Malignant ovarian lesions; Uterine myomas.

Introduction

Ovarian malignant neoplasms are the most common gynaecological pelvic malignancies in most Western countries [1]. The advent of vaginal ultrasound screening methods for ovarian cancer has made the ovaries more accessible. Dramatic changes in ovarian tissue vascularity during oncogenesis are mediated by numerous angiogenic factors and can be detected by using flow data from color Doppler [2]. Malignant tumour vessels are usually dilated, saccular, and tortuous, and may contain tumour cells within the endothelial lining of the vessel wall. Ovarian lesions, like any other living tissue, emit spontaneous magnetic activity caused by ionic movements across the plasma membrane. Ovarian cancer mortality rates, measured as 5-year survival, have not changed over the past 50 years despite significant advances in screening methods [1, 2]. It is tempting therefore to use novel technology in order to achieve a better understanding of oncology.

Breast cancer is a major health problem. The worldwide incidence of the disease is increasing by 1.5% per annum. Despite many detailed epidemiological studies including a large number with biological measurements, the etiology of breast cancer remains unclear [3]. Over 700,000 new breast cancers are diagnosed worldwide each year. Screening programs involving periodic physical examination and mammography in asymptomatic and high-risk women increase the detection rate of breast cancer and may improve the survival rate. Unfortunately most women who develop breast cancer do not have identifiable risk factors and analysis of epidemiologic data has failed to identify women who are not at significant risk and would not benefit from screening. New less expensive screening techniques such as two-view mammography are being investigated in an attempt to reduce the cost of widespread screening [4, 8]. Breast, like any other living tissue, generates alternative magnetic fields as a result of the continuous ionic micro-currents across the plasma membranes. Their magnitude depends on the functional state of the tissue. The more intense the breast dynamics the higher the magnetic fields produced.

Uterine myomas irrespective of whether they are small and asymptomatic (as in the postmenopausal women) or large and symptomatic (as in premenopausal women) considerably affect uterine artery blood flow velocity. Circulation of benign uterine leiomyomas has been described by use of Doppler velocimetry [9-12]. Much higher blood flow velocities were recorded in the arteries of large myomas than in small ones. Uterine artery blood flow velocity reflects uterine perfusion, and low uterine artery PI values might originate from the need for increased blood supply in uteri with large myomas as a consequence of the increased uterine volume. Doppler velocimetry studies on myoma vessels (both capsule and core vessels) have shown that PI values < 1.0 are common in uterine myomas and do not indicate malignancy [11]. This eliminates the role of Doppler studies in the discrimination of benign uterine myomas from other malignant pelvic tumours.

The SQUID is a diagnostic tool capable of measuring the exceedingly weak magnetic fields emitted by living tissues. The higher the concentration of living cells in the test area, the higher the biomagnetic fields produced and recorded from it. This non-invasive technique has been used successfully for the differentiation of breast and ovary benign and malignant diseases and uterine myomas [6-12].

Methods

Biomagnetic recordings were obtained by a single channel second order gradiometer DC-SQUID (MODEL 601; Biomagnetic Technologies Inc., San Diego, CA) [6-12]. During the recording procedure the patient was relaxed lying on a wooden

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bed free of any metallic object so as to decrease the environmental noise and get better signal to noise ratio. Ultrasound scanner Doppler examination assessed prior to the procedure the exact placement of the target area in order to be sure that the biomagnetic signals from nearby vessels were excluded. The recordings were performed after positioning the SQUID sensor 3 mm over the exact position of the target area assessed by the Doppler examination in order to allow the maximum magnetic flux to pass through the coil with little deviation from the vertical direction. Five points were selected for examination according to the lesion topography. Point 5 was located at the very center of the lesion, whereas points 1-4 were located at the periphery of the target area. For each point 32 recordings of 1-sec duration each were taken and digitized by a 12 bit precision analogue-to-digital converter with a sampling frequency of 256 Hz. The duration of the above recordings is justified because the chosen time interval is enough to cancel out, on the average, all random events and to allow only persistent ones. The biomagnetic signals were bandpass filtered, with cut-off frequencies of 0.1-100 Hz. The associated Nyquist frequency limit, with the above-mentioned sampling frequency, was 128 Hz, which was well above the constituent frequency components of interest in biomagnetic recordings and avoids aliasing artifacts. Conversion of the analog signals into digital recordings was accomplished by means of an AD converter on line with a computer. The average spectral densities from the 32 signals of magnetic field intensity were obtained using Fourier statistical analysis. By convention, the maximum value was used when assessing the lesions. The obstetricians were ignorant of the biomagnetic values [6-12].

The biomagnetism of breast lesions

Sivridis *et al.* [6] investigated the biomagnetic activity produced physiologically by the various normally occurring states of the female breast: puberty, reproductive age, pregnancy, lactation and menopause. Biomagnetic activity was low at puberty (105.46 ± 3.77 fT/√Hz) and the menopause (111.66 ± 25.06 fT/√Hz), but was high during the reproductive years (142.13 ± 20.70 fT/√Hz), particularly in the hyperplastic states of late pregnancy (221.86 ± 12.14 fT/√Hz) and lactation (252.73 ± 54.77 fT/√Hz). The results were statistically significant ($p < 0.0001$, ANOVA).

Anninos *et al.* [7] investigated the biomagnetic activity obtained in benign and malignant breast lesions. Magnetic recordings were obtained from 21 patients with palpable breast lumps. Of these 11 were invasive carcinomas and ten were benign breast lesions. They used non-linear analysis to investigate whether there is any biological differentiation in the dynamics of these two types of lesions. High amplitudes characterized the waveform of a malignant breast lesion whereas in benign ones the corresponding amplitudes were low. Using the application of non-linear analysis they observed a clear saturation value (8.23 ± 0.35 fT/√Hz) for the dimension of malignant breast lesions and no saturation for benign ones.

Anastasiadis *et al.* [8] investigated the spontaneous magnetic activity generated from 24 palpable breast lumps: of these 19 were invasive carcinomas and five were benign breast lesions. The age of the patients with malignant tumors ranged from 42-64 compared with a range of 33-43 for patients with benign breast disease. The magnetic fields recorded in the 2-7 Hz frequency range were of high amplitudes in malignant breast neoplasms (754 ± 305 fT/√Hz) and of low amplitudes in benign breast disease (274 ± 49 fT/√Hz). This difference was statistically significant (t-test, $p < 0.005$) and there was no overlap between the values obtained from the two types of breast lesions.

The biomagnetism of ovarian lesions

Anninos *et al.* [9] investigated the biomagnetic activity in benign and malignant ovarian lesions using non-linear analysis. Magnetic recordings were obtained from 21 patients with palpable ovarian lesions. Of these ten were invasive carcinomas and 11 were benign ovarian lesions. The exact nature of these lumps was determined histologically. They observed a clear saturation value around 6 for the dimension of malignant ovarian lesions and no-saturation for benign ones.

Anastasiadis *et al.* [10] investigated the biomagnetic activity in benign and malignant ovarian diseases. Magnetic recordings were obtained from 40 patients with palpable ovarian lesions. Ninetheen of these were invasive carcinomas, and 21 were benign ovarian lesions. Interestingly, the ovarian lesion waveforms and the corresponding spectral densities were of high amplitude in most (96%) malignant ovarian lesions, and of low amplitude in most (95%) benign ones. These findings were of statistical significance (t-test, $p < 0.005$).

The biomagnetism of myomas

Anastasiadis *et al.* [11] studied the hemodynamics of the uterine artery myomas by use of Doppler ultrasound and biomagnetic measurements. Twenty-four women were included in the study. Sixteen of them were characterized with large myomas whereas eight of them with small ones. Biomagnetic signals of uterine artery myomas were recorded and analyzed with Fourier analysis. The biomagnetic signals were distributed according to spectral amplitudes as high (140-300 ft/√Hz), low (50-110 ft/√Hz) and borderline (111-139 ft/√Hz). Uterine artery waveform measurements were evaluated by use of the Pulsatility Index (PI) (normal value $PI < 1.45$). There was a statistically significant difference between large and small myomas concerning the waveform amplitudes ($p < 0.0005$) and the PI index ($p < 0.0005$).

Kotini *et al.* [12] investigated the non-linearity in the biomagnetic recordings of uterine myomas. Twenty-four women were included in the study. Sixteen of them were characterized with large myomas and eight with small ones. Uterine artery waveform measurements were evaluated by use of the PI (normal value $PI < 1.45$). Applying nonlinear analysis to the biomagnetic signals of the uterine myomas, they observed a clear saturation value for the group of large ones (mean = 11.35 ± 1.49) whereas no saturation for the small ones.

Discussion

It is well known that tumour hyperemia is related to new blood vessel growth as well as to dilatation of previously existing vessels. Viable tumour cells release diffusible angiogenic factors, which stimulate new capillary growth and endothelial mitosis in vivo even when tumour cell proliferation has been arrested by irradiation [13]. There is strong evidence that growth of solid tumours beyond a few millimeters in diameter depends on the induction of functional microcirculation from the surrounding host tissue. It is obvious that malignant tumour induces growth of an independent and characteristic vascular network on its own. The tumour vasculature is highly heterogeneous and does not conform to standard normal vascular organization. A key difference between normal and tumour vessels is that the latter are dilated, saccular and tortuous, and may contain tumour cells within the endothelial lining of the vessel wall [14, 15].

The malignant tissues, by virtue of their rapid expansion and vascularity have increased ionic movement and therefore produce magnetic fields of higher intensity than slower growing benign tissues. The differences reported are apparently due to malignancy itself and are not influenced to any extent by other factors such as the size of the tumor, the proportion of fat to glandular tissue, or the depth of the lesion within the mammary gland. The size of the lesion per se seems to have very little influence on the recordings obtained. Equally, if there was to be any interference from the fat tissue surrounding the lesions, this should have an adverse effect on the magnitude of values obtained for the group of older patients, i.e. those with malignancies, since the proportion of fat to glandular tissue increases with advancing age. Undoubtedly, the closer the lesion to the skin surface the greater the values recorded, but there was no evidence that malignant lesions were lying more superficially than benign abnormalities.

The data presented in the studies [6-12], although preliminary, justify a novel approach to biomagnetism and suggest that this method of measuring the magnetic activity of ovarian and breast diseases and uterine myomas can be potentially exploited in differentiating tumours. This is not unexpected as malignant tissues, by virtue of their rapid expansion, vascularity and thus increased ionic movements produce magnetic fields of higher intensity than normal tissues. Therefore, more studies in larger series and further technological innovation of the equipment used need to be done before the method can be established as a screening procedure in clinical practice.

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