Ultrasonic Examination of the Breast
Edited by J. Jellins and T. Kobayashi


# DOPPLER STUDY OF BLOOD FLOW IN BREAST CANCER

J. C. Bamber, M. Sambrook, H. Minasian and C. R. Hill

Institute of Cancer Research: Royal Marsden Hospital, Sutton, Surrey, UK.

## INTRODUCTION AND BRIEF REVIEW OF DOPPLER STUDIES OF BREAST CANCER

An ability quantitatively to assess tumour vascularity and blood flow in patients may be significant for prognosis, measurement or early assessment of response to therapy, and improvements in the diagnostic procedure. The Doppler ultrasound method of monitoring blood flow transcutaneously is remarkable in being suitable for routine and repeated use on patients. Furthermore, it is possible to selectively explore the flow and the Doppler signals can be processed to yield quantitative results, give details of flow direction and make images of the spatial distribution of flow.

Published use of Doppler ultrasound for breast investigations appears to have begun in 1977 and has proceeded with 6 fully published studies to date (Wells et al. 1977; Gros et al. 1978; Zypacewicz et al. 1978; White and Cledgett 1978; Burns et al. 1981; Minasian and Bamber 1982). Apart from our own work, all of these studies have been concerned with the detection of breast cancers by the characteristic Doppler signals to which they give rise. The descriptions of the signals given by the various authors, although different in detail, broadly suggest that in tumours, relative to normal and benign breast tissue, there is more blood, flowing faster and simultaneously in many different directions. A so called "characteristic sound" to the Doppler signals from tumours seems to be associated, at least in part, with a high flow rate which persists through diastole and on which is superimposed a low amplitude high frequency systolic modulation. All but one (Burns et al. 1981) of these diagnostically oriented studies dealt with very small numbers of patients (9-24). No impalpable cancers were studied and most of the analysis of the information was accomplished qualitatively by ear. Nevertheless, encouraging results were obtained. In a series of 55 cancers among 404 symptomatic women, it appeared that 96% of malignant and 84% of benign lesions were correctly classified by a subjective analysis of their Doppler signals alone. (Burns et al. 1982).

Following such demonstrations that the Doppler method can detect the blood flow associated with malignant breast tumours we began a study of the blood flow of normal and malignant mammary tissue with a view

to increasing our understanding of breast cancer biology and possibly improving the clinical management or diagnosis of the disease. In the more short term we were also interested to know if endocrine therapy could cause early detectable changes in tumour blood flow and if such changes could be related to therapeutic response. Results from the first 16 patients studied have already been reported (Minasian and Bamber, 1982). In the remainder of this paper we present results from the 24 patients that have now been studied and some preliminary data obtained in an attempt to document any changes in normal mammary blood flow which take place during the menstrual cycle and pregnancy.

## METHODS

The diseased and normal breasts of 1 pre-menopausal and 23 post-menopausal patients with proven breast cancer, and both breasts of 9 pre-menopausal volunteers (normal and not using oral contraceptives) have been studied. Ten of the cancer patients were receiving endocrine therapy and were examined repeatedly over a period of several months. The volunteers were examined repeatedly over one or more menstrual cycles, or over the course of pregnancy. Our apparatus and the method of its use to permit the quantitative study of relative blood flow characteristics of the breast have been described before (Minasian and Bamber, 1982). Briefly, the system consisted of a 10 MHz, continuous wave, direction resolving Doppler flowmeter, a maximum frequency follower, headphones and a stereo tape recorder which had been modified to permit its recording level to be calibrated in absolute terms. Between 3 and 6 sites of strong, high frequency signals were selected over the tumour, or one normal breast in the case of a volunteer. Repetition of signals derived from the same artery was avoided. Signals from "mirror-image" sites on the contralateral breast were also recorded. A system was developed, using marked transparent acetate foils placed over the breast, for repeating these measurement sites on subsequent occasions, and adjustments of the skin-probe angle were always made to obtain the highest possible Doppler shift frequencies. Estimates of tumour volume were obtained by assuming a spherical shape and using the average of 4 diameters measured by palpation.

We are currently working to establish a permanent data analysis system involving a real-time digital spectrum analyser linked directly to a computer. As a temporary measure, and for the preliminary results presented here, two different systems have been used. The recordings associated with patients were analysed as described previously (Minasian and Bamber, 1982), by averaging (about 5 cardiac cycles) manually taken readings of A, the maximum frequency at peak systole, and B, the maximum frequency at end diastole, from the frozen display of a digital spectrum analyser. Features such as the mean ((A+B)/2), range (A-B), pulsatility index (range/mean), and A and B themselves, were then averaged over all the sites on a given breast. Some of the recordings from the volunteers have been analysed by a different method, as follows. Lacking an audio-frequency (A.f) spectrum analyser of our

own,* but possessing equipment for and experience in radio-frequency (R.f.) spectrum analysis, we constructed a hybrid system which is depicted in use in fig. 1 (Bamber and Phelps, 1981). The analogue time compression memory shown in fig. 1 contains 4 analogue shift register memories (2 x Fairchild CCD 321A) which have a common audio input and a sampling rate of 29 KHz. The samples stored in each memory are clocked out at about 7 MHz. Sequential output from the 4 registers produces R.f. pulses at a rate of 2 KHz, each one contributing a point on the sampled Doppler spectrum displayed by the R.f. spectrum analyser. Compromises in the performance specifications of this combination are possible, depending on the choice of clock rates, frequency scan rates, etc. For the data discussed here the system was set up to produce a 40 point spectrum covering the frequency range 0 - 7 KHz every 20 ms. The 3dB bandwidth (frequency resolution) and maximum dynamic range were approximately 725 Hz and 22 dB respectively. For these data the time varying spectrum was displayed continuously for 10 to 15 cardiac cycles whilst being photographed with an open camera shutter on polaroid film. This resulted in an integrated spectrum, the outline of which represented the maximum amplitude spectral envelope. From this outline, which was traced using a graphics tablet linked to a microcomputer, various features were derived. These included the maximum systolic frequency ($f_{max}$), the mean and modal frequencies over the cardiac cycle, and the integral (A) of the power in the spectrum after normalization with respect to the recording level. As with the previous method, features extracted were averaged over all sites on the same breast or volunteer.

## RESULTS

The addition of another 8 cases to our previous results has not greatly altered the main trends observed, which can be summarized and brought up to date by the following statements. The averaged characteristics of Doppler signals from untreated malignant breast tumours were always different from those obtained from the normal breast in the same patient, and provided confirmation of the descriptions in the literature. Averaged values for the mean frequency, for example, were 2.2 ± 0.9 KHz (1 St. dev.) for all tumours, and 1.1 ± 0.4 KHz for the normal breasts of these patients. The average of the difference between mean frequencies (tumour - normal) was 1.1 KHz, the smallest difference being 0.05 KHz and the largest 3.4 KHz. For the post-menopausal patients a strong positive correlation was observed between the Doppler characteristics and the tumour volume, the extrapolated "zero volume" value for the mean frequency having a value equal to that of normal breast tissue. Fig. 2 is an updated graph of these data and also demonstrates that a slight improvement in the measure of association between these variables is obtained if the data are first operated on with a geometric transformation
(r linear = 0.73, r geometric = 0.77 , where r is the correlation

*The above mentioned analyses were possible because of the kind co-operation of P.N.T. Wells et al. at the Bristol General Hospital.

coefficient). The value obtained for the one pre-menopausal patient was uncharacteristic of the rest of the data and was omitted from the correlation analysis.

The major changes in blood flow to breast tumours during endocrine therapy appear to occur in association with, and possibly slightly in advance of, changes in tumour volume. We have not yet discovered any advantage in using blood flow as a measure of tumour response although possibly useful small changes in flow, which occur early during treatment, require a greater number of subjects before their significance can be assessed. Figs. 3, 4 and 5 represent examples of the three categories of behaviour which are observed following therapy, i.e. definite response, continued growth, and a limited response which is not sustained.

Examples of data obtained during the menstrual cycle and pregnancy are provided in figs. 6, 7 and 8. In fig. 7 the dependent variable was obtained as the product $Af_{max}$ averaged over all measurement sites and normalised to the average value at mid-cycle. We believe this to be one of a number of combined amplitude x frequency parameters which, given that a variety of factors (such as depth of blood vessel and tissue attenuation coefficient) remain fairly constant during the study, represent a relative measure of fluctuations in blood volume flow rate.

## DISCUSSION

This study is still in progress to the extent that data on more tumour cases are being acquired and the existing data are currently undergoing a more detailed analysis. Meanwhile, as a supplement to the conclusions drawn in our previous publication, the following observations can be made.

The non-linear fit to the data of fig. 2, if significant, perhaps makes more sense than a linear relationship if one expects to observe a manifestation of the known development of ischaemic centres during tumour growth. If the use of Doppler methods for the diagnosis of small or non-palpable breast cancers is to be proposed then it is to be hoped that the vasculature of small tumours does not display the characteristics predicted by extrapolating our data to small tumour volumes. A study of such "early" cancers is required to settle this question.

A thorough discussion of the results of measurements on the volunteers must await the analysis of data from 4 other subjects for whom data was gathered more frequently and over 3 menstrual cycles. Nevertheless the observed periodic fluctuation in blood flow to the breast during the menstrual cycle, and the continued increase with gestational age during pregnancy, would appear to be significant. The timing of the rise in mammary blood flow - just before or around the onset of menstruation - is consistent with the time at which there is a maximum in the total circulating levels of estrogen, progesterone and prolactin (Moore, 1971), with measured variations in

breast surface temperature (Simpson et al. 1981) and with the timing of the cyclic mammary hypertrophy and breast pain which sometimes occurs (Cutler, 1961).

The observation that the hormonal status can measurably influence the Doppler parameters suggests that more meaningful data, and better discrimination of pathology, might be obtained if the effect were accounted for in future studies of pre-menopausal patients. Using the contralateral breast as a control for tumour studies may well be sufficient to achieve this. A knowledge of the natural variations in breast blood flow might also be helpful for optimizing the timing of breast surgery or therapy by drugs and, if the presence of a tumour alters these fluctuations, for early diagnosis of breast cancer.

## REFERENCES

Bamber, J.C. and Phelps, J.V., 1981. Unpublished, but details available from the authors.

Burns, P.N., Halliwell, M., Wells, P.N.T., and Webb, A.J., 1982. Ultrasonic Doppler studies of the breast. Ultrasound Med. Biol., 8, 127-143.

Cutler, M., 1961. Tumours of the breast, Pitman Medical Publishing Co., London, p.20.

Gros, C.R.M., Dale, G., and Geirand, B., 1978. Breast echography : criteria of malignancy and results, in Recent Advances in Ultrasonic Diagnosis (Ed. A. Kurjak), Excerpta Medica, Amsterdam, pp 292-298.

Łypacewicz, G., Powalowski, T., and Łukawska, K., 1978. Ultrasonic examinations of breast tumours with Doppler method, in Proceedings of the Second Congress of the Federation of Acoustical Societies of Europe (Eds. L. Filipczinsky and J. K. Zieniuk), Vol.II, Polish Academy of Sciences, Warsaw, pp 153-156.

Minasian, H., and Bamber, J.C., 1982. A preliminary assessment of an ultrasonic Doppler method for the study of blood flow in human breast cancer. Ultrasound Med. Biol., 8, p. 357-364.

Moore, W.W., 1971. Endocrinology of reproduction, in Physiology, 3rd Ed. (Ed. E. E. Selkurt), Little, Brown and Company, Boston, pp 801-809.

Simpson, H.W., Mutch, F., Giles, C., Grant, J.K., Griffiths, K., Halberg, F., MacEwan, J., McNicol, A.M., Turbitt, M., and Wilson, D., 1981. A fresh approach to human breast cancer, in Commentaries on Research in Breast Disease 2 (Eds. R. D. Bulbrook and D. J. Taylor), Alan R. Liss, Inc., New York, pp. 133-164.

Wells, P.N.T., Halliwell, M., Skidmore, B., Webb, A.J., and Woodcock, J.P., 1977. Tumour detection by ultrasonic Doppler blood flow signals. Ultrasonics, 15, p. 231-232.

White, D.N., and Cledgett, P.R., 1978. Breast carcinoma detection by ultrasonic Doppler signals. Ultrasound Med. Biol., 4, p. 329-335.

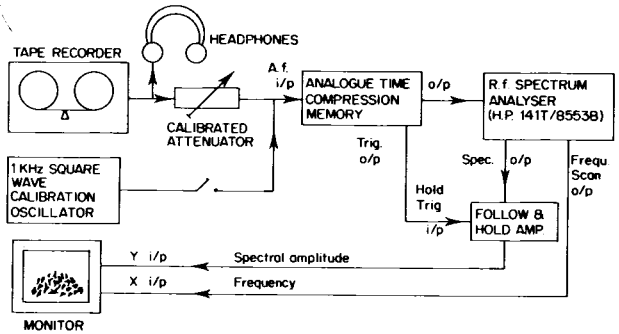


Fig. 1. Hybrid system permitting the use of an R.f. spectrum analyser in the audio frequency range.

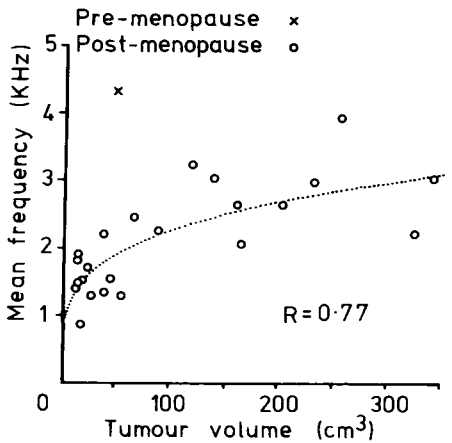


Fig. 2. Variation of the mean Doppler shift frequency with tumour volume for 24 patients with primary breast cancer.

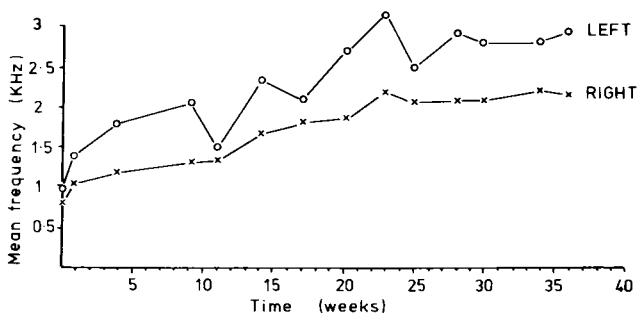


Fig. 8. Variation in blood flow characteristic, mean Doppler shift frequency, of the normal breast during pregnancy (1 volunteer)

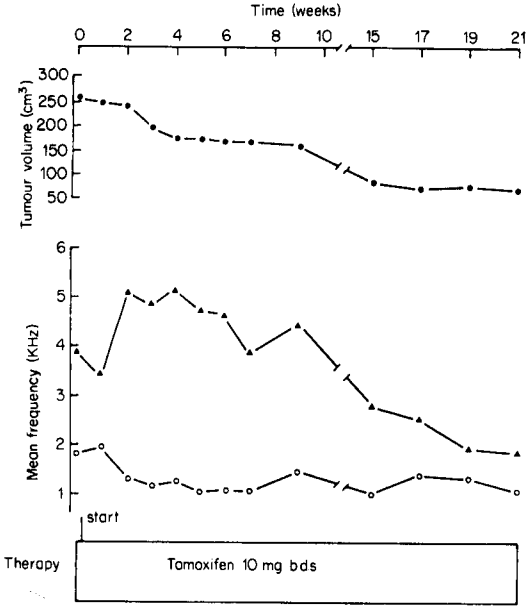


Fig. 3. Example of complete response to endocrine therapy.

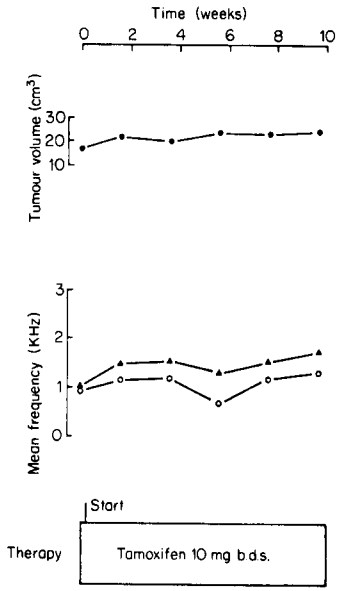


Fig. 4. Example of no clear response.

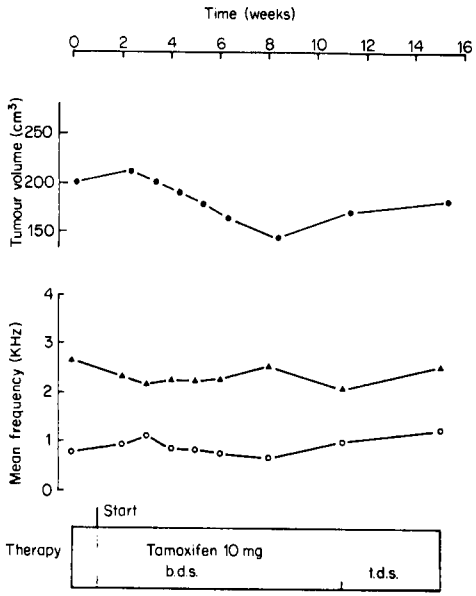


Fig. 5. Example of a transient response.

Key to figs. 3, 4 and 5 : ▲ = measurements from tumour sites, o = measurements from normal sites on the contralateral breast.

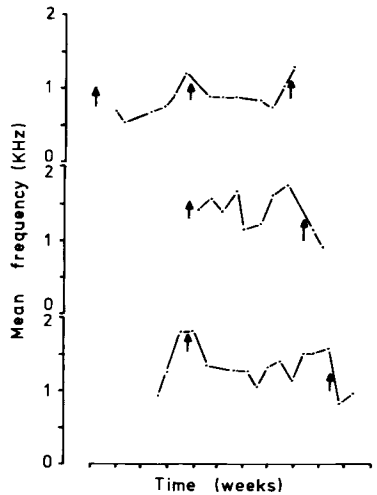


Fig. 6. Blood flow characteristic, mean Doppler shift frequency, of the breast during the menstrual cycle (3 normal volunteers). ↑ = time for onset of menstruation.

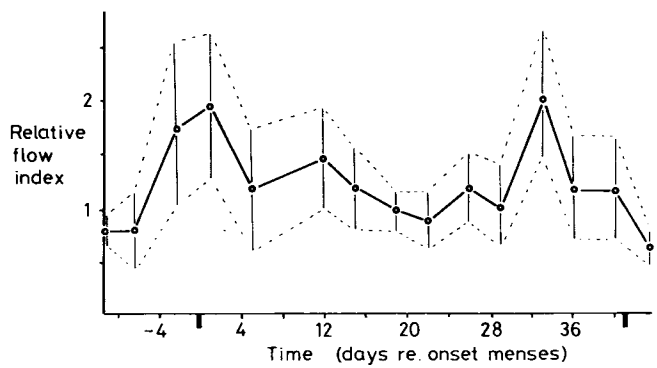


Fig. 7. Example of mammary blood flow for one normal volunteer, over the duration of one menstrual period (mean and ± 1 St. dev. for 7 sites). The "relative flow index" is $Af_{max}$ (see text), where the value from each site has been normalized to the average value mid-cycle before computation of the errors.