Current Statement of Electrochemotherapy in Bulgaria

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Abstract: *Electrochemotherapy is one fast, easy, effective and safe method for treatment of patients with clinical and cytological diagnosis of skin tumors as Carcinoma basocellulare, Carcinoma spinocellulare, Kaposi sarkoma and Mycosis fungoides in stage I (T1N0M0). Therapy is based on the temporary formation of pores on the surface of the cell membrane, resulting from the application of electric field with appropriate intensity and duration trough which the cytostatic drug as bleomycin is introduced into the tumor cells. This work presents data on the last version of electroporator and the treated patients by the method electrochemotherapy recently.*

Keywords: *Electrochemotherapy, Skin tumor, Bleomycin, Savety electroporator, QRS synchronization.*

Introduction

For the last years it has become necessary to find global innovative approaches for solving the problems of the aging populations and the countries with some economic problems. The epidemiological data for cancer point out that the skin tumors are the most spread cancer diseases in the industrial countries of Europe. With the exception of the malignant melanoma, the skin cancer is the most encountered tumor in Bulgaria: 33.7 of every 100 000 people (statistical information from Specialized Hospital for Active Treatment of Oncology – Sofia). This is due to a complex of factors – geographical, climatic, ecological etc. The frequency of this disease has been growing in the last years particularly at the age of 60-80.

One of the main goals of the biological and medical sciences is to increase the effectiveness of the cancer treatment.

Electrochemotherapy became a powerful method for tumor treatment and gene delivery during the past decades [6, 11, 15, 16]. However, there are a lot of unsolved problems related to the instrument design and the fundamental studies concerning the local increase of the anticancer drugs in the tumor tissue.

Most of the known instruments for electrochemotherapy are large in size, heavy to carry and have no optimised possibilities both for scientific studies and routine practice.

Some of previous experience in electrical stimulation of innervated muscles [4] suggested that biphasic stimuli were of better tolerance. That is why in old apparatus, developed by Daskalov and coworkers [3] a new type of biphasic electrical pulse sequence was introduced for electrochemotherapy, resulting in improved efficiency and toleration by patients [7, 12, 17, 21]. In addition, bidirectional electrical field might induce permeabilisation of a greater number of tumour cells. The enhanced effect of biphasic pulses applied at higher frequencies was subsequently proven by independent theoretical and experimental studies of other authors [1, 10, 13, 14].

Equipment

A) Electroporators

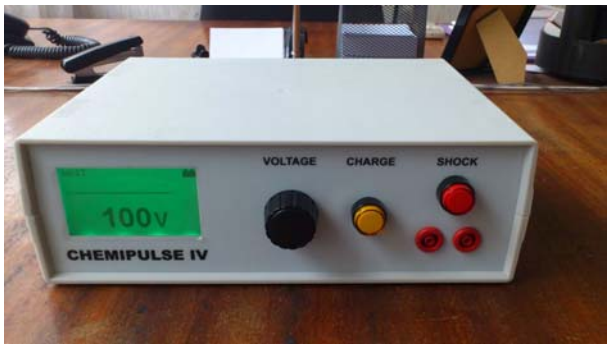
The portable electroporators named by us *Chemipulse III and IV* (Fig. 1A, B, C) are an improved version of the high voltage generator that was introduced by Daskalov et al. [3, 7]. The pulse transformer was optimized after studying the allowed compromise between the technologically provoked 1) non-ideal leading and trailing edges of the pulses, and 2) unavoidable pause between the positive and negative parts of the biphasic pulses on the one hand, and the efficiency of the biphasic sequence on the other. Exceptional means warranting the electrical safety of both patient and physician are provided. The electroporator is battery supplied. Additional circuit automatically disconnects the applied part from the instrument as soon as the charging device (adaptor) is coupled. The pulse sequence is generated by high voltage capacitor, which is charged from the battery immediately before the shock. The amplitude is selected gradually from 100 V through 2200 V but the pulse sequence cannot be activated if the voltage choice does not start from the lowest level. Thus the risk of involuntary provoked electroshock with unsuitable energy is eliminated. Once selected, the electrical charge is available to be applied on the patient not more than 10 s. After that an automatic discharge is accomplished, if the physician has not started the shock.

The electrochemotherapy is accompanied with unpleasant sensations because of the contraction of muscles around the electrodes. These sensations are reproduced with every pulse of a train of pulses if the frequency of repetition is low. Daskalov et al. [4, 7] drew attention that they can be smoothed down to only one if the pauses between the pulses are shorter than the duration of a tetanic contraction. In such case the nerve axon cannot be excited for the refractory period. That is why in new version the number of pulses was increased with 8 pulses. This pulse sequence has been optimized during long series of clinical tests with companion animals [9, 18-20]. It was shown that the use of trains of biphasic pulses enhances in vitro and in vivo the cytotoxic effect of doxorubicin on multidrug resistant colon adenocarcinoma cells [9].

Electroporators give 16 biphasic rectangular pulses, 50 + 50 μs duration each, with a 20 μs interval between both phases and a pause of 880 μs between the bipolar pulses. The new instrument is with battery supply, enhanced protection against electrical hazards both for the patient and the physician, autonomy providing for more than 200 shocks with one battery

charging. The data could be used to support the optimization of the voltage shock setting and the evaluation of the procedure effectiveness.

A) B)



C)

Fig. 1 A) *Chemipulse III* coupled with the module for long-term recording of pulse parameters during treatment of surface tumors; B) hardware QRS detection accomplished in real time by the QRS synchronizer; C) *Chemipulse IV* electroporator and QRS synchronizer in one body

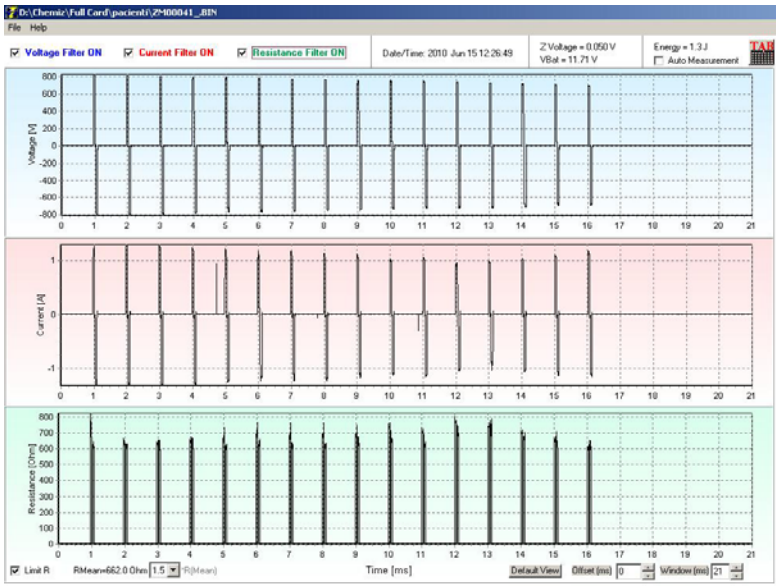
The electroporation pulse parameters are recorded by a precise Chemipulse Recorder, which allows the applied during the electroshock voltage and current to be saved and analyzed together with the patient resistance, determined immediately before, during and after the procedure.

The measuring module is connected between the electroporator and the patient. Special measures are taken for:

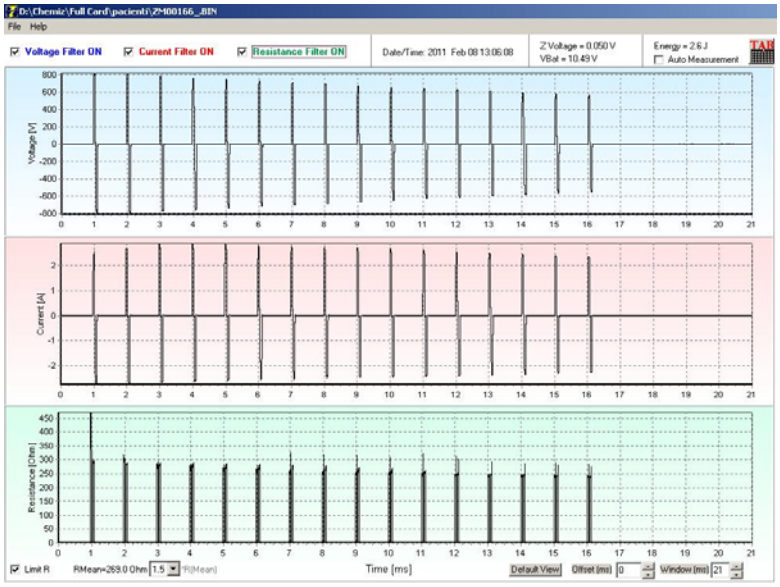
1. increasing the electrical safety of both patient and operator provided by battery supply;
2. high accuracy achieving by 12-bit ADC with adjustable sampling rate up to 5 MHz;
3. long term storage of all measured data and signals.

The generated current is measured by means of serial connected low resistor (0.1 Ω). The voltage value is obtained through high resistant divider. The parameters of the measuring circuits are harmonized to have no influence on the parameters of the selected high voltage pulses (up to 2000 V and 10 A). The resistance is calculated as relation between the measured voltage and current.

Appropriate software is developed for automated pulse measuring and visualization (Fig. 2A and B).



A) parameters of electrotreatment of patient with Ca basocellulare located on the nose



B) parameters of electrotreatment of patient with Ca basocellulare located on upper back

Fig. 2 Pulses record of an applied voltage, current and resistance

B) Electrodes for electrochemotherapy

The electrodes were a pair of parallel stainless steel wires of 0.8 mm in diameter and 15 mm of length (Fig. 3). The interelectrode distance was adjustable (calliper type) in the range of 5-30 mm. The threshold sizes of treated tumours were 30 mm in diameter. Lesions bigger than 30 mm were treated with radiation and/or chemotherapy. The size of the lesion was measured by calliper instrument (Arimedex). Good contact between electrodes and the skin is ensured by a conductive gel.

Fig. 3 Electrode for electrochemotherapy type caliper

C) QRS synchronization

Mali et al. [8] examined the influence of electroporation pulses on heart functioning. They observed that the transient interval between two consecutive R waves decreases after the treatment the authors concluded that a synchronized electroporation would increase the patient safety in cases of anatomical locations presently not accessible to the existing devices and electrodes [8].

Shortly, a pulse generation immediately after the QRS detection will be the most reasonable approach. Details about technical and hardware decisions are given in Dotsinsky et al. [5]. The electroporator and QRS synhronisator in *Chemipulse IV* were incorporated in one body. The equipment with QRS synchronizer is mandatory in cases of electrochemotherapy of patients with pacemakers and patients with heart problems.

D) Module for long-term recording of pulse parameters

It is designed a module for data collection of the pulse parameters and the impedances of treated patients with surface tumors (Fig. 1A upper block and Fig. 2). The data could be used to support the optimization of the voltage shock setting and the evaluation of the procedure effectiveness of electrochemotherapy. The collection of data of impedance could permit one personal approach for electrotreatment of tumors.

Electrochemotherapy of skin tumors

A) Patients

All patients included in this trial are with clinically and cytologically verified diagnosis Carcinoma basocellulare (Ca basocellulare), Carcinoma spinocellulare (Ca spinocellulare), Kaposi sarkoma, Mycosis fungoides, in stage I (T1N0M0) and the application and study of electrochemotherapy in patients was approved by the ethics committee of the hospital and all patients gave written information consent before beginning treatment. All treatments were carried out at Dermatologic Clinic at Specialized Hospital for Active Treatment of Oncology, Sofia.

Mycosis fungoides is not typical skin cancer. This disease is related to the skin T-lymphoma, which in itself is a low-grade malignant lymphoma with 3 clinical phases of the disease. The first stage is expressed by premycosal eruptions and tumour-like formation and is initiated by a generalized and constant skin itching. Erythemas and urticaria-like rashes appear and are later transformed in erythema-squamos infiltrations. Sometimes the lesions are like swellings. In the former our study 29 lesions of histologically verified 1st stage of Mycosis fungoides were successfully treated by electrochemotherapy with interferon – α [13].

The patients were selected according to the following conditions:

- diagnosis confirmed by cytology;
- informed consent to acceptance of the type of treatment, including comparison with other treatment modalities of the disease;
- post-treatment follow-up of at least 12 months.

The treatment response was evaluated at least 4 weeks (one month) after the treatment according to WHO guidelines as follows: 1) complete response (CR): the absence of any trace of tumour; 2) partial response (PR): decrease in the tumour volume by 50% or greater; 3) no change (NC): decrease of less than 50% or an increase of less than 25% in the tumour volume; 4) progressive disease (PD): tumour volume enlarged more than 25%.

B) Anesthesia and drug

We injected intralesionally anesthetic 1 ml (lidocaine 1%) and Bleomycin 1 ml (Bleocin Nippon Kayaku Co., Ltd, Japan) into the tumours. Before the anesthesia all tumors were measured and photographically saved. The field intensity was in order of 800 – 1000 V/cm. When the tumors are placed near the mucous tissue or the cartilage the field intensities were lower, because the places are very sensitive to pain.

C) Side effects

Sometimes the temperature after electrochemotherapy increases until 38-39°C, but with analgetics could be reduced. The temperature increases is only in the frame of 24 h after electrotherapy. Single side effects after electrochemotherapy are erythema and slight edema at the side of the treated lesions occurred in most of the patients and disappeared in a few days, one week at most.

D) Patients monitoring

Because more of skin tumors are on the visible places of the body (predominately on the face) and to take biopsy after electrochemotherapy will give some scars. To monitor non-invasively the effects of electrochemotherapy spectral analysis – light induced autofluorescence spectroscopy was used. Autofluorescence spectra are taken from the lesion and surrounding healthy skin, prior to, immediately after treatment and at the control check-ups [2]. The method could be applied as a very precise tool for initial diagnostics, for planning and monitoring of therapeutic procedures.

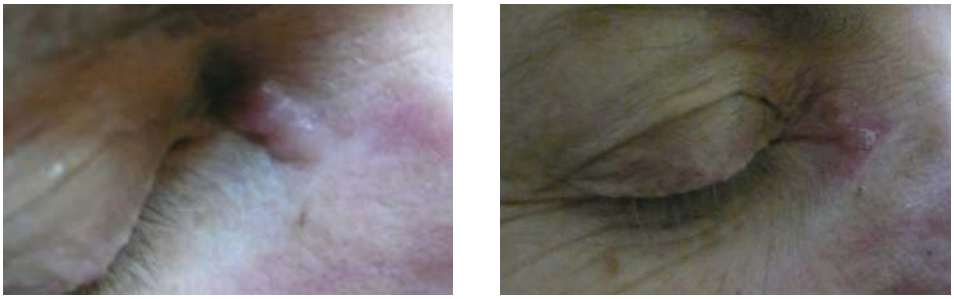
Results from electrochemotherapy

Since 2010 year 44 patients with 47 lesions are treated by electrochemotherapy with new version of *Chemipulse III* and *IV* at the presence of antibiotic bleomycin or interferon. Some patients have more than one lesion. The ages of patients are between 28 and 85 and the number of male (M) is 23 and female (F) – 21.

The biggest number of skin cancers is Ca basocellulare (Table 1A) and only one with Ca spinocellulare (Table 1B).

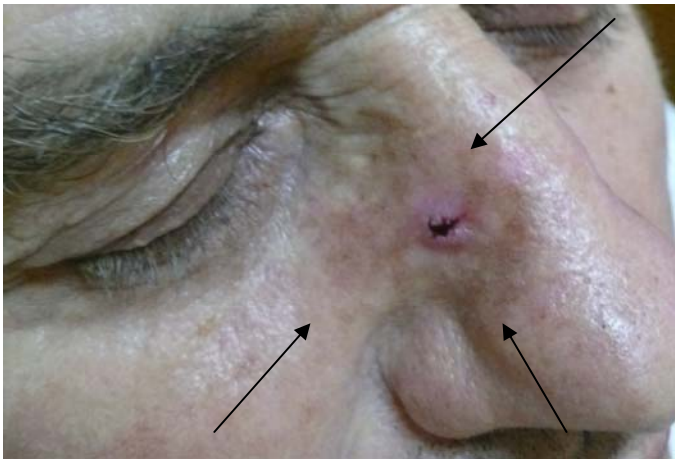
The field intensity was considered taking into account some parameters: the longest length, place and conciseness of the lesions. The applied field strength was lower when the lesions were near to the spinal column. Low field strengths were used in cases when the lesions were on the face (on the cartilaginous tissue) or near to the mucous tissue to avoid necrosis and pain.

In one month, when electrochemotherapy were applied some change in the volume, pigmentation, epidermal atrophy or lack of scars was observed (Fig. 4).

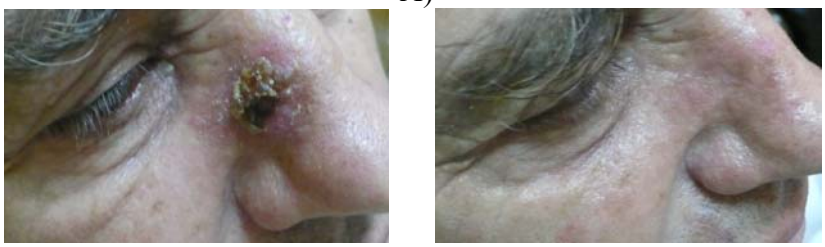


A) B)

Patient No 1: A) before treatment; B) one month after treatment

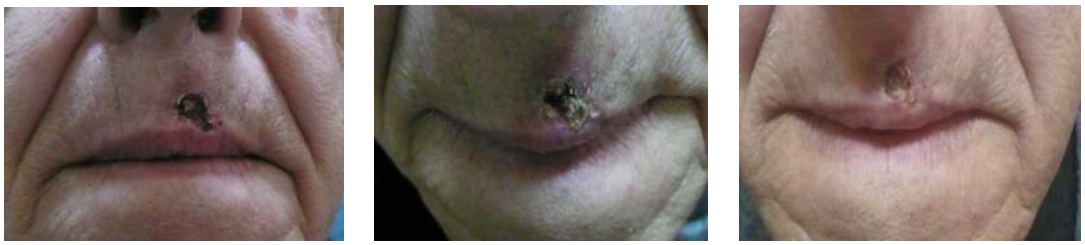


A)



B) C)

Patient No 2: A) patient before treatment (recurrence of tumor after surgical treatment); B) one week after electrochemotherapy; C) one month after treatment – the scar is not visible



A) B) C)

Patient No 3: Ca basocellulare on the lip: A) before the electrochemotherapy; B) one week after treatment; C) one month after therapy

Fig. 4 Some representative cases of patients with Ca basocellulare

Patients (No 5, 9 and 10) were treated second time and there were no signs of recurrence up to the end of the follow-up period. The patients No 14 and 33 were in stage NR and they were directed to the standard radiotherapy. Patients (No 18, 21, 23, 27 and 32 from Table 1A and No 1 from Table 1B) were treated with electrochemotherapy after recurrence of tumors after surgical treatment. Patient No 21 was with big lesion and the electrotreatment was done by 2 burst of pulses, applied on crosswise. At these cases the electrochemotherapy is very useful because the scars will be not increased. After surgical recurrence the field strength was lower (about 800 V/cm), because the inflammation as a secondary side effect could damage the tissue.

No patients with cardiac pacemakers were treated during this period. Patient No 15 was with cardiac problems (aortic aneurysm).

The treated patient with Ca spinocellulare is in stage CR (Table 1B). As a rule at Ca spinocellulare could occurred some relapses but due to the very low number of treated patients the recurrence was not observed.

Table 1 A. Patients with Ca Basocellulare electrochemotherapy with Bleomycin

No	Gender, age	Location	Dimensions, [cm]	Voltage, [V]	Answer	Follow up, [months]
1	F, 62	Nose	0.6	800	CR	24
2	F, 54	Forehead	1.0	1000	CR	24
3	M, 71	Nose	0.6/0.1	800	CR	24
4	M, 79	Back	1.01	800	CR	23
5	M, 73 treated second time	Upper lip	1.0	800	CR	8
6	M, 60	Forearm	1.0	800	CR	20
7	F, 77	Neck	0.9	600	CR	20
8	M, 74	Back	1.0	600	CR	20
9	F, 48 treated second time	Nose	0.5	600	CR	12
10	F, 81 treated second time	Beck	1.05/0.82	800	CR	12
11	M, 65	Back	0.13/0.21	1000	CR	18
12	F, 81	Cheek	2/2.5	1000	CR	18
13	M, 74	Leg	1.68	800	CR	18
14	M, 85	Back	2.71/2.47	1000	NR	1
15	M, 80	Back Back Back sacral	0.85 1.73 0.8 1.1 2.54	800 800 400 700 600	CR CR CR CR CR	16 16 16 14 4
16	M, 38	Back	0.82	800	CR	15
17	M, 68	Beck	0.95	900	CR	12

18	F, 60	Eyebrow recurrence after surgical operation	0.77	600	CR	8
19	F, 53	Lumbo-sacral	0.21/0.14	950	CR	8
20	M, 70	Sacral	2.52	800	CR	8
21	M, 52	Breast recurrence after surgical operation	1.9/1.0	600/300 crosswise treatment	CR	8
22	M, 70	Nose	0.7	400	CR	3
23	M, 28	Cheek, recurrence after surgical operation	1/0.5	500	CR	8
24	F, 78	Forehead	1.3	890	CR	9
25	F, 44	Nose	1.2	890	CR	9
26	M, 50	Cheek	1.4	900	CR	9
27	F, 57	Cheek recurrence after surgical operation	1.0	900	CR	9
28	M, 72	Nose	1.0	900	CR	9
29	F, 76	Cheek	1.0	900	CR	9
30	M, 57	Cheek	1.0	900	CR	9
31	F, 64	Cheek	0.5	600	CR	9
32	F,47	Nose, recurrence after surgical operation	0.5	600	CR	9
33	M, 65	Back	0.75	900	NR	1
34	F, 64	Back	0.43/0.67	800	CR	9
35	F, 88	Back-sacral	0.89	800	CR	9
36	F, 74	Cheek	0.8	600	CR	9
37	M, 44	Nose	1.1	300	CR	9
38	M, 80	Forhead Nose	0.15/0.25 1.1	500 700	CR CR	9 9

Table 1 B. Patient with Ca Spinocellulare and electrochemotherapy with Bleomycin

No	Gender, age	Location	Dimensions, [cm]	Voltage, [V]	Answer	Follow up, [months]
1	F, 63	Cheek recurrence after surgical operation	1.0/0.5	300	CR	5

During the period of investigation only three patients with Sarcoma Kaposi were treated by electrochemothepay with bleomycin and all are in stage CR (Table 2).

Two females with Mycosis fungoides and diabetes were treated with interferon – α. In both cases the patients are in CR for 9 months (Table 3). In their case some chemotherapy or surgical treatment is not recommended because of strong inflammation and additional a green wound, that could occurred.

Table 2. Electrochemotherapy with Bleomycin of Sarcoma Kaposi

No	Gender, age	Location	Dimensions, [cm]	Voltage, [V]	Answer	Follow up, [months]
1	F, 80	Forearm Forearm	0.92 1.22	500 500	CR CR	21 21
2	M, 73	Toe	0.6	500	CR	16
3	M, 82	Hip Hip	1.3/0.7 1/0.5	1000 1000	CR CR	9 9

Table 3. Patients with Mucosis fungoides and electrochemotherapy with interferon – α.

No	Gender, age	Location	Dimensions, [cm]	Voltage, [V]	Answer	Follow up, [months]
1	F, 53	Leg Leg	1.35 1.95	700 700	CR CR	5 5
2	F, 57	Leg	3.57/2.51	700/700	CR	5

Conclusions

It was developed equipments *Chemipulse III* and *IV*, consisting of portable electroporator, QRS synchronizer (in one body) and module for long-term recording of pulse parameters. QRS synchronization could prevent the occurrence of arrhythmia or ventricular fibrillation.

The electrochemotherapy is an effective, inexpensive and mostly single procedure for treatment of skin tumors without hospitalization of the patient.

Forty four patients with a total of 47 lesions of Ca basocellulare, Ca spinocellulare, Kaposi Sarcoma and Mycosis fungoides were treated with electrochemotherapy using intralesional application of bleomycin or interferon – α. The scars disappear after electrochemotherapy in one month. The method is very suitable for patients with diabetes, with skin cancers after surgical operations and the recurrence of lesions. Erythema and slight edema at the site of the treated lesions occurred in most of the patients and disappeared in a few days, one week at most.

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Professor of Biomedical Engineering Mikhail Matveev is Vice Director (Head) of Institute of Biophysics and Biomedical Engineering, Bulgarian Academy of Sciences. He holds the degrees of M.Sc. in Nuclear Physics, Computing Mathematics and Ph.D. in area of Medicine. His research interests are in the medical microprocessor systems and devices; biomedical data and signal processing and analysis; basis sciences in cardiology; pattern recognition; medical decision support systems; risk assessment and medical decision making; classification procedures in medicine.
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