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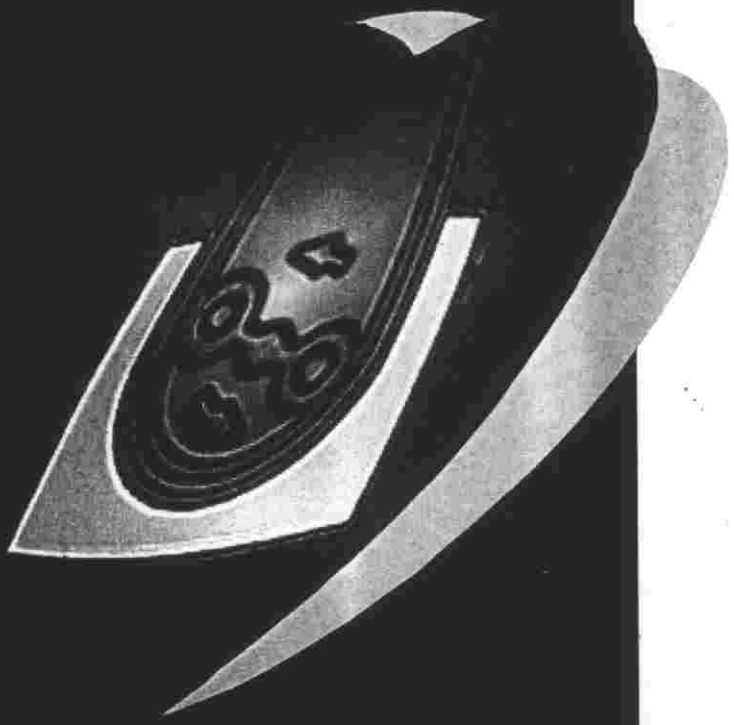

Spedizione in abb. post. art. 2 comma 20/b - legge 662/96 - Filiale di Firenze

ASSOCIATO ALL'UNIONE
STAMPA PERIODICA ITALIANA

Vol XV n° 1
Maggio 2003

IN BY PASS - Vol XV n° 1

COMPUTERIZATION AND ELECTRONIC INTEGRATION IN THE OPTIMIZATION OF BIOMEDICAL SYSTEM FOR THE HYPERTHERMIC ANTIBLASTIC PERFUSION IN EXTRACORPOREAL CIRCULATION

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Keywords: chemotherapy, hyperthermia, perfusional technique, limb tumour

In the last years, new technologies allowed the working out of safety, flexibility and interactivity monitoring systems in oncological treatments. These events leaded us to improve the system of extracorporeal circuits and of supervising instruments during locoregional perfusional treatment in closely controlled hyperthermia.

A Reference Technical Group (RTG) was appointed in order to establish the critical requirements of perfusional treatments in oncology and to describe technical requirements of a perfusional system.

The RTG, consisting of surgeons, engineers, physicists and technicians, contacted many biomedical Industries to consider the existing systems.

At the end of a fine verification a firm, producing a perfusional system with particular features, was identified. On the basis of that a technical-scientific collaboration, between RTG and company, was started. The cooperation has produced some corrections in order to adjust the requirements to our need.

First of all our study addressed the optimization of technological innovation of the locoregional antiblastic hyperthemic perfusion of the limb because this treatment is more critical but technical features are requirements of quality apply to the others locoregional perfusional procedures.

Hyperthermic treatment: definition. The starting point of the RTG study has been the definition of features of a hyperthermic treatment. These rules are well known, but they can not be forgotten or omitted when are going to introduce a new element in the limb-circuit system.

The definition of target temperature and active phase is the first part in a correct hyperthermic treatment. In the treatment of advanced melanoma of the limbs, the current protocol requires the use of melphalan and true hyperthermia (range: 41.5-41.8 °C) (1-7). In soft tissue sarcomas the prevalent schedule of therapy is the association between TNFa-melphalan and mild hyperthermia (8-9). The duration of active phase is very important because it shows the length of the treatment when the target temperature achieves. In advanced melanoma, the active phase goes on 60 minutes (10-15) whereas in sarcoma, it persists for 90 minutes (16-17).

The thermal uniformity is another critical parameter of procedure. An efficacious treatment needs an uniformity of the head distribution (*uniformity in space and in time*). In other terms, the whole perfusive district (i.e. all tissues in the limbs) (18-19) must be between 41.5-41.8°C, in each moment of the active phase (20). The most important thermic values are expressed by limb-probes, while the circuit-probes must be correlatable and not be higher to 42.0°C, because higher values could bring about proteinic denaturalization (21-24).

Minimal requirements for the system: After the identification of physical criteria of the treatment the RTG has studied equipments to an exact monitoring and an effective realization of procedure.

Our knowledge, derived from our clinical experience lasting for 20 years now with about 300 patients treated through selection from a collection

of about 700 that were examined for eligibility, shows that the thermic uniformity in space is only possible in adiabatic ambient: various experiments and theoretical analyses we have performed demonstrate that the requirement of a fast-responding, accurate and uniform temperature distribution can only be satisfied by designing a heat-delivery apparatus capable of preventing heat transmission from the limb to the external ambient as much as possible. Our technique involves wrapping completely the limb inside a warm-water blanket kept at the target temperature, in addition to feeding the perfusate at the same temperature (16-18). The careful realization of an adiabatic ambient is an important element of the hyperthermic procedure.

Other relevant aspects regard the biomedical system used for the treatment. The device must be reliable in every action during the procedure, but it must excel at temperature monitoring and heat exchange.

Up to today, the temperature measurement accuracy and reliability have been managed by resorting to redundancy and frequent calibration verifications. This philosophy, though proven to be technically adequate, is binding and tiresome for the staff and can be in some aspects in conflict with the recent strict safety regulations.

The device must be handy. The electronic and computer science evolution should had to take advantage to produce user-friendliness interfaces. So the device would be able to a quick response and easy use.

The computer powerful is able to provide a graphic or numeric display of monitoring data, facilitating their interpretation and their registration.

The communication between biomedical device and PC is essential. The quantity of data is impressive if it is manual controlled but it is poor for a computer manipulation. Therefore, during the minimal requirements codification, the RTG did not judge important the information about a particular link (RS232, USB, IEEE1394 and so on) because the less quick connection is also effective (with the advantage that it is also cheap).

Computer must import data in a compatible format with the common software because the compatibility reduces the costs of design and of production and subsequently it is a quick learner. This facilitates the data distribution and the communication between departments performing multicenter studies.

The computer powerful has not to lead into temptation to produce an automatic control system of the procedure. *The entire system operation must remain under direct control of the medical staff at all times.* Possible partial closed-loop controls of the treatment must be evident in their presence and principle of action and when needed it should be possible to cut or overrule their activity without consequences for the physical control or the data flow.

Other important requirements, when planning the acquisition of clinical material, are the compatibility with international standards and directives such as those published by the European Economic Community (EEC) and the International Electro-technical Commission (IEC). The EEC published in 1993 the Medical Device Directive (MDD - 93/42/EEC), which came into force in all member States in 1998. The MDD describes the minimal, mandatory, requirements to which any medical device must demonstrate conformity to be sold in the European market.

Conformity of the System needs adequate electric insulation of he parts, in contact with the patient and immunity to the external electromagnetic disturbances. The electric insulation must be proportional to system voltage (i.e. a device with a supply of 220 volts must have a minimal electric insulation of 1500 volts).

Every biomedical device must have got a protection with respect to the conditions of "single fault" (i. e. the guarantee of safety even in the presence of a faulty part, which in our case this implies, for instance, that all microprocessor-controlled operations must be guaranteed, such as by doubling the numerical control devices or adding batteries to avoid stopping voltage).

We invite you to study the European Law about a greater quantity of information.

The process initiated by the MDD, while on one hand showing promise of better quality, reliability and safety, on the other hand is demonstrating to represent a serious challenge for the small-size manufacturers and/or for the production of devices and pieces of apparatus with limited diffusion but which cannot be dispensed with in the medical applications. As a result, some manufacturers may decide to desert the European market or to abandon products for which the CE marking costs make the prospective selling returns unattractive.

Industrial manufacturing. At the end of essential requirements coding for a system for locoregional hyperthermic treatment, RTG started to look for an above-described system in national and international biomedical industry.

Rand (S.r.L.) was contacted because it produces a supported integrated system for locoregional perfusional treatment (Performer LRT)

We performed some visits to Industry to examine the assembly and check line and to carry out some simulating tests of treatment.

The functional proof was regular: the system was efficient but it needed some additional requirements.

So the RTG required Industry some modifications to improve some technical features about:

1) **Circuit configuration**:
   a. increase in reservoir capacity to six liters: this assures a valid use of the system with the other perfusional treatment;
   b. bubbles trap (compulsory in American Law): it is an additional security system because a membrane oxygenator is integrated in the circuit;
   c. inlet and outlet tubing are protected with thermal isolation because a temperature drop as low as a few tens of a °C it is allowed.
2) **Tubing configuration**: we advised to modify the section of inlet line (artery) to _ of an inch and the pumping section to 3/8 of an inch to guarantee 1200 ml/minutes (maximum flow). The increase of the outlet line to 3/8 of an inch guarantees a good venous return (it occurs to drop).
3) **Temperature monitoring**:
   a. necessity to monitor at least eight external temperatures: one probe at the oxygenator, one at the inlet and outlet of the patient (these three probes are integrated into the circuit and so are disposable) and five probes are used to monitor the temperatures of the tissues of the district under treatment;
   b. possibility to use various probe configurations for example: needle probe to monitor the muscle, subcutaneous and so on, surface probe to monitor the skin, the peritoneum and so on, esophageal and tympanic probe to monitor the system temperature during abdominal hyperthermic treatment;
   c. possibility to use thermocouple or thermistor probes because the thermocouple probes are longer and finer than thermistor and so are better in the deeper monitoring.

Conclusions. The Industry (RanD S.r.L.) has modified the system on the basis of our suggestion witt the exception of the possibility of the use of thermocouple probes. These probes are not compatible with the European Law because of an inadequate electric insulation. So the use of these probes would compromise the electric insulation of the whole system. This problem was postponed waiting for the thermocouple probes are compatible.

The *in vivo* tests, performed for the hyperthermic antiblastic treatment of the limbs and for the abdomen, demonstrated efficiency, safety and manoeuvrability of the system.

The learning curve of the medical staff has been enough quick for the efficacy of course performed at Industry head office, for the full manual and for the clarity of the user-interface.

The data presentation is efficacy, we see a useful graphic display of the limb temperatures in function of the time (FIG 1), moreover it is possible an easy crossing between graphic and numeric display. In numeric display the System shows temperatures, flows and pressures. This simplicity makes easer the procedure control and so the safety is better.

The system saves data every one minute and it allows data transfer, at the end of the procedure, to PC a RS232 connection. Saved data are temperatures, flows, pressures, any warning, default data and time. These data give a picture of the treatment *a posteriori*. Automatically, a Microsoft Exel® macro provides for data transmission and for graphic processing of all parameters in function of time. This automation allows at medical staff a saving time and an easy use of data.

An internal printer lets a drawing up of a report with patient's personal particulars, temperatures and time. This document makes easy the upgrade of clinical memorial.

The system is compact and so it is easy carried and it is not much bulky.

In conclusion it is desirable that other Institutions will adopt this system because data exchange, their interpretation and multicenter studies will be facilitated.

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