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Mini Review

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Neonatal and pediatric general and cardiac anaesthesia and icu: what's new in 2017/2018? -bari pediatric hospital experience-italy

Abstract

This review wants to give an overview to most of the controversial fields in the clinical therapeutic assistance in neonatal and pediatric general and cardiothoracic surgery in anaesthesia and pre or post-operative Intensive Care Unit Treatments.

This is a report of the protocols and studies, published or still on the way to be validate, in the Neonatal and Pediatric General and Cardiac Anaesthesia and ICU of a Pediatric Hospital in Bari-Italy.

Even though science is very fast in giving to clinicians devices and new therapeutical goals, it is the clinicians themselves who have to use them in a correct way or, at least, in an alternative way, always taking in mind the patient safety.

This is how we daily act: we try to adapt the new devices or drugs to the patient's problems and not the patients to them, keeping in mind that the development of dedicated systems in neonatal and pediatric age is very difficult to reach.

In the last few years we have adapted some of the adults techniques to neonate and pediatric patients, after parent's consent signed, trying to open new pathways in several different pathology treatments and in anesthesia Haemodiafiltration and new blood purification techniques for septic shock and sepsis treatment, use of new procoagulative factors in neonatal cardiac surgery, validation of a new non invasive bio-impedenzometric program and devices for a total control of cardiovascular status applicable to premature and neonate, new miorelaxant and antidote use, sedation in ICU, Pediatric TCI developments, are the targets of our daily work.

Keywords: inflammatory response, cytosorb, plasmapheresis, ecmo, provertinum, miorelaxants, dexdemetomidine, nica's, neonatal and pediatric tci

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Abbreviations: VAD, ventricular assistance devices; ECMO, extracorporeal membrane oxygenation; CVVHDF, continuous veno venous hemodiafiltration; CARPEDIEM, cardio-renal pediatric dialysis emergency machine; WBEB, whole body electrical bioimpedence; TEB, thoracic body bioimpedance; ICG, cardiac impedenzometry measures

Introduction

Neonatal and pediatric SIRS and Sepsis and Septic Shock are still at risk of high level mortality, especially when these events are followed by a Multi Organ Disfunction and cardiovascular acute failure.

Very frequently these are the results of a not well known or treated infection, which could be both microbial or viral, of a congenital or acquired immunologic deficiency or are related to particular conditions of the patient's treatment as immediate or late post-operative period, post-operative period after extracorporeal circulation for cardiac surgery, cardiovascular or respiratory deficit treatment with extracorporeal devices as Ventricular Assistance Devices (VAD) or Extracorporeal Membrane Oxygenation (ECMO).

Many progresses have been done in antibiotics therapy and in organ support; Continuous Veno Venous Hemodiafiltration, (CVVHDF) or new pediatric dedicated and gently working dialysis machine as Cardio-renal Pediatric Dialysis Emergency Machine (CARPEDIEM),[1] are very useful for the clinicians to threat such potential deadly conditions.

The VAD support in cardiac failure and the Respiratory/ Cardiac ECMO support are very helpful since they give time to organs suffering from dysfunction (MOF) to recovery, but in most cases this treatment approach requires highly skilled performers, is very expansive and presents, in neonatal and pediatric population, many adverse events.

Many studies in literature have the proposal to understand the limit between therapeutic goals and therapeutic over treatments; and this limit is very difficult to be reached.

There is a common pathway in the expression of many of these problems which is the not complete knowledge of the Human Inflammatory Response; a direct consequence of this reality is that, especially in neonates and pediatric patients, it is very difficult to uniform the treatments and to have dedicated devices.

In the late 2000 we started to threat the Inflammatory Response in vivo or in vitro situations using routinely the haemodiafiltration techniques such as CVVHDF, CRRT, and CVVH in many specific diseases or viral pathologies as Guillain –Barrè syndrome or viral and bacterial meningoencephalitis this is our first therapeutic step.[2]

In addition, in the aim to increase the modulation of the inflammatory response and decrease the amount of circulating cytokines, in the last 6-7 years we have completed the treatment with an intermittent plasmapheresis application.

In order to quickly modulate or remove the aggressive organic functional response to inflammation, we were used to perform a plasmatic apheresis using fresh frozen plasma but, in the last three years we have changed the plasma with albumin.[2]

A clinical evidence of better results has been shown comparing the result of this treatment with the data of a historical group receiving a conventional treatment.

The golden standard has been reached with the use of Cytosorb Absorber that seems to be very effective in reducing the amount of circulating citokines in a faster way. At the moment a pilot study is on the way in our unit.

The study is not only related to the control of inflammatory response in sepsis, septic shock, but we are using the "Cytosorb Absorber" even during cardiac surgery REDOU procedures to control bleeding, and ECMO procedures.

Bleeding in neonatal and pediatric cardiac surgery can be a very difficult complication to control. In neonatal surgery it mostly depends on organ immaturity and more frequently on the use of Prostaglandine E1, as well as, last but not least, on complications derived from cyanosis and cyanotic pathology.

Currently, we are evaluating a new strategy of medical bleeding, treating the patients with a new Factor VII Human Derived (Provertinum). A first data analysis seems to be very reassuring, while a double blind study is on its way to be started.

Sedation of neonate and pediatrics patients is important. There are many different opinions and protocols concerning the necessity to sedate very young patients in ICU since many drugs need to be used to perform it in the best way.

There are many delicate conditions where sedation can't be aggressive in order to avoid cardiovascular and neurological destabilization. In neonatal and pediatric cardiac surgery this is compulsory. The use of dexdemetomidine seems to be helpful in this sense although drugs could cause cardiac depression or bradycardia.

The monitoring of the cardiovascular condition in a pediatric patient is not that easy especially if we want to perform it using not-invasive methods.

Therefore in our unit we have validated the algorithm for a new not invasive pediatric device that considers the variation of bio-impedenzometric values using only two ecg plaques sited on the left and right forearm or left and right ankle of the patient. The validation of the algorithm has been done for patients weighting less than 30 kg and could be easily used in premature and neonates as well.

Starting from the author personal long experience and collaboration with Prof. Gavin NCG Kenny since the late 1995 in the study, application, development and use of pediatric Target Control Infusion System (TCI) to give anesthesia to zero-weighting and zero- aged patients, during the last year we have pointed out and tried to build up a new theoretical version of pharmacodinamic and pharmacokinetic action at the biophase for anesthetic drugs.

It seems to me highly remarkable that after Absalom Kenny and Lal "Pedfusor", Mionto's and Kataria's studies there hasn't been any significant development in the use of Pediatric TCI.

In my personal opinion, it depends on the fact that to develop a new pediatric TCI system it is strictly necessary to abandon the normal and modern pharmacological concepts and outline and identify a new GEPTS thricompartimental equation which applies to different pharmacological concepts (Figures 1-2).

Our golden point is to study the patient's response to the anesthetic drugs action and its actual slope-curve in cells which have a very fast growth, as the neonatal and pediatric human cells do.

"Allometric Laws" could be useful and very effective in building up a new theoretical Thricompartmental equation.

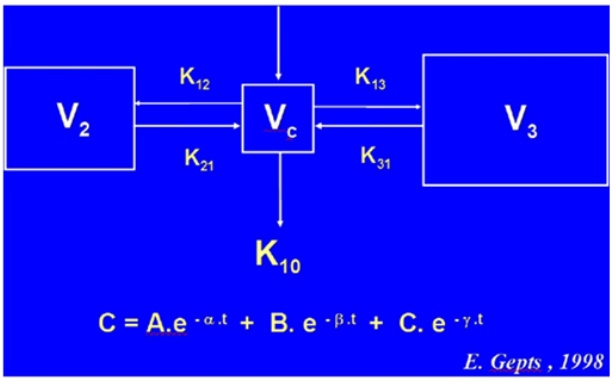

Figure 1 Gepts Thricompartimental Equation.

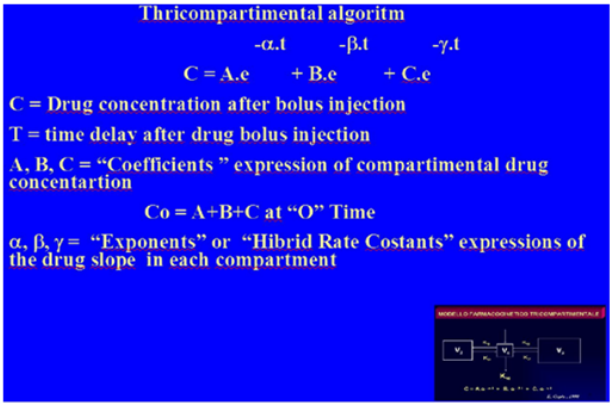

Figure 2 Gepts Thricompartimental Equation.

Procedures and methodology of application

Cytosorb Absorber

The Cytosorb Absorber (Cytosorb Europe GmbH, Berlin, Germany), as we already said, is a new medical device able to remove in a very short time citokines weighting from 10 to 50 kDa.

It is a high-porosity polimer with a biocompatible surface able to chain citokines and remove the majority of them from the circulating blood.

We must consider that the weight of most of the circulating citokines during inflammatory response varies from 10 to 50 kDa.

This device is registered only for adults weighting >40 kg and not for a pediatric use.

There is enough literature regarding the use of Cytosorb and its usefulness in adult patients' treatments but not so many articles regarding its pediatric use.

In middle 2016 in our unit we first used Cytosorb Absorber to treat a pediatric case of Haemophagocitic Hystiocitosys in "Imminentia Mortis" of the patient with excellent results.

The levels of mioglobine, citokines and C5a active complement fraction decreased in the first 12 hours of application.[3]

We asked the Ethical Committee for a pilot study,[4] (at the moment data results are under analysis) and we obtained the authorization to use Cytosorbe in similar cases (ETHICAL COMMITTEE 53891-2017).

The excellent clinical results we noticed encouraged us to use Cytosorb none only to threat SIRS, Sepsys and MOF related to infections but also in threating the inflammatory response due to the in vitro reological blood and immunity changes as it happens during procedures like ECMO, VAD or during surgical Bleeding (Figures 3-5).

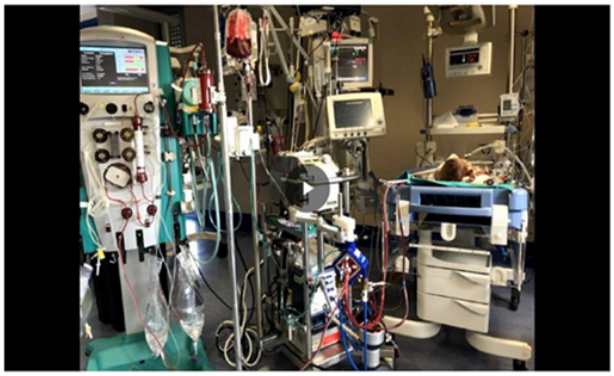

Figure 3 Cytosor, CVVHDF, Plasmapheresis in neonatal cardiac patient.

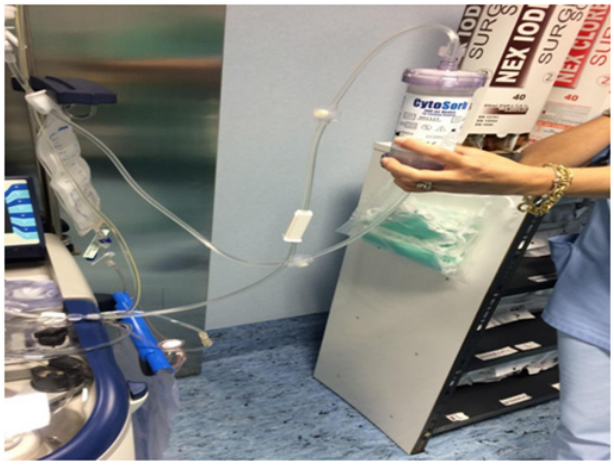

Figure 4 Cytosorb application to blood surgical field recover device.

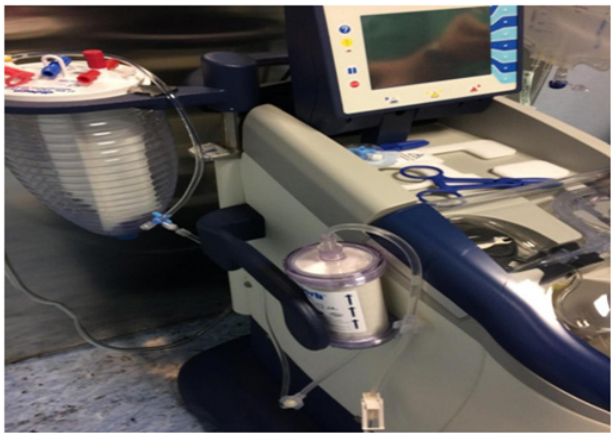

Figure 5 Surgical recovery blood device with sited Cytosorb.

According to the compared data analisys of historical patients, we had an important reduction in surgical bleedings during REDOU in cardiac surgical procedures such as Fontan procedures or conduit replacements. Although we can confirm that clinical bleeding and infective events are reduced even in ECMO patients we are aware that further communications and studies will be required.

We are very confident with the first examination of data coming from the pilot study; we examinated the citokines levels in blood before, during and after Cytosorb application and the results concerning the reliability of Cytosorb application seem to be very effective.[3]

In our opinion the main target is to create a neonatal and pediatric device which could reduce the cytosorb priming volume and its flow rate but first of all it is compulsory for us to outline the right time of the cytosorb's application when it is used together with others extracorporeal purification devices.

Clinical Bleeding Treatment

The clinical bleeding is generally an important adverse event during surgery but it could have even worst catastrophic consequences in particular situations as neonatal or pediatric cardiac surgery, with a major risk in reinterventional surgery (REDOU) procedures.

Many times bleeding is a consequence of surgical "maneuver" that can start up Disseminated Intravascular Coagulation (DIC like syndrome).

The use of heparin to anticoagulate a patient under cardiopulmonary by-pass to permit surgery, can actually increase the clinical bleeding.

The same effect can have Hypothermia as consequence of a surgery performed in Cyanotic Patients.

We conducted the control of coagulation and anticoagulation during By-pass or ECMO or cardiocirculatory extracoporeal assistance with a coagulative combinated diagram that takes in account the data from Activated Coagulation Time (ACT) and the data from Tromboelastogtaphy (TEG).

These unusual combinations avoid us from the need of laboratory coagulative tests, give us an almost complete view of the causes of bleeding and permit us to act directly over them.

Even tough, in many cases, the reintegration of coagulation semisintetic factors, especially in neonates, is very difficult and not permitted, it is not even enough in bleeding effective control, even in presence of blood red cell, plasma, albumin refillin, to have a complete and satisfactory result due to the necessity to have the patient in By-pass or ECMO anticoagulated.

It is a very hard to reach the right balance between coagulation and anticoagulation, especially in long -term application period.

After the permission of parents we administred,in an "OFF LABEL" authorized mode, a new Human Plasma Derived VII Factor ("Provertinum-Baxalta") to neonate and pediatric patients during ECMO procedures or cardiac surgery postoperative period with excellent results.[5]

Provertinum acts chaining the Hunman Tissue Factor and the complex acts activating factor X and factor IX; so that in presence of correct levels of prothrombine, the coagulation pathway is reconducted t to a more normal function.

We are used to administer adequate doses of protrombine before starting Provertinum infusion or bolus administration.

There is no standardized dosage of this factor and we administer it in a TEG-ACT guided way.

The TEG control is compulsory for us in order to avoid a serious complication of the Provertinum administration which is the possibility, in case of overdosage, of a dangerous procoagulant activity.

Citation: Milella L. Neonatal and pediatric general and cardiac anaesthesia and icu: what's new in 2017/2018? -bari pediatric hospital experience-italy. *J Pediatr Neonatal Care*. 2018;8(1):1–6. DOI: 10.15406/jpnc.2018.08.00309

The target is to reach a correct Reaction Time ® a correct Couguli Formation Speed in time; a gently prolonged time (K), and aA value (Angle value) gently diminished value at TEG diagram.

A double blind study request has already been submitted to the Ethical Committee.

Miorelaxants

The use of miorelaxant drugs in premature, neonatal and pediatric anaesthesia or in ICU is still controversial. Several opinions strongly confirm that in prematures and neonates it has to be avoided. There is a controversial about the receptorial anatomical structures in prematures and neonatal patients.

Another argumentation is related to the damages that eventually a miorelaxant can produce even to normal anatomical receptors in neonates and toddlers.

In my opinion, some of these argumentations are correct and can be reliable for those procedures that take place in countries where miorelaxants, such as succinilcoline, are still used, or when a combination of rapid and long acting miorelaxant drugs are needed to perform a surgical procedure.

On the other hand, new molecules that can change the point of view of the miorelaxant strategy in theatre or ICU are now in commerce.

First of all the receptor for miorelaxants in neonate and premature patients is nowadays clearly defined : 5 capsomeric receptorial proteins constitute the receptors; 2 alfa, 2 beta and 1 theta chain are present in neonates instead of 1 gamma chain present in adult patients. The difference between the two chains is that Theta chain leads to a rapid depolarization of the receptor while the Gamma chain is dedicated to an intermediate and long duration depolarization

It is also well known that in the first 24-48 hours of life, the Theta chain changes its anatomic structure becoming a Gamma chain and the whole proces is completed in the first week of life.[6]

This complex process leads to the development of a new intermediate action miorelaxant as Vecuronium Bromide and a new miorelaxant action reversal, Sugammadex, which actis in a different way than phisostigmine or prostigmine or suxametonium.

The use of sugammadex is not permitted under two years of age.

This is apparently a serious problem that we are trying to overtake.

From 2014 until nowadays we have been using Vecoronium Bromide and Sugammadex to perform every kind of anaesthesia at any age and weight of the patients.

It was possible thank to an "OFF LABELL" use procedure, but to support our decision we demonstrated[7-9] that this combination of drugs is very useful in very difficult intubations[4] and particularly in those situations where the cardiovascular stability is a compulsory goal.[7,8]

We have demonstrated that sugammadex can be used as a saving life antidote since it is able to reconduct a spontaneous breathing in less than 60 seconds after injection.[9] Sugammadex protects anesthesiologists in case

of a missed intubation, a complicated muscular relaxation without any possibility to perform a good assisted ventilation (as per syndromic and plurimalformated patients) [9] and in case of drug overdosages.

The mechanism is actually complete and fast and, last but non least, every vecuronium bromide molecola is removed from circulating blood because it is inglobated in a lipofillic protective wall without any possibility to recirculate and relock the receptor. There is no possibility of late ricurarization.[6]

Dexdemetomidine

An adeguate and personalized sedation in neonates and pediatrics patients is becoming a consistent part of the therapeutic treatment in ICU stay.

It is necessary to split up the different typologies of anesthetic procedures in a combined anesthesia from the sedation set up required by a ICU stay patient. Expecially in cases of long stay patients. Our unit is part of SARNePI Study Group of sedation for neonate and toddlers.[10]

Many drugs are used in different ways according to the patients requirements.

There is not a single specific protocol to be followed due to the very different tipology of patients we take care of in our ICU.

We can say that the target is unique, in terms of reduction of ansiety and fear, but even pain cannot be controlled without a good sedation set up.

Our first goal is to reach a low patient humoral and neuroendocrine response during the stay in ICU without any disturbance related to ventilation, respiratory physiotherapy and cardiovascular stability.

Our protocols consider the contemporary use of differents drugs, benzodiazepines, neuroleptic drugs, morphine, ipnotic drugs and the intermittent changing of association between them.

In the last two years we have considered the use of dexdemetomidine as a valid option to new and old sedative drugs. Our first concern was referred to the apparent important impact of dexdemetomidine over the cardiovascular system and cardiac inotropic and cronotropic expression.[10]

We have studied the application of dexedemetomidine to post-operative cardiac surgery patients[10] and a double blind study has been proposed to EC, but the daily application of the use of drugs is giving us the impression that dexdemetomidine cardiovascular impact is not so deeply adverse to a cardiovascular stability. We assume it is related to a different dosage, lower than the suggested one, and to the fact that each patient receives a different sedative or hypnotic drug depending on his clinical history. Further studies are required.

NICaS (non invasive cardiac system)

NICaS is a new not invasive cardiovascular control system (NICaS-NI PETACH TIKVA-Tel Aviv University-Israel).

The device is already used in adults but there was no algorithm for neonate and toddlers application.

There is a lack of devices in commerce able to measure in a not invasive mode the cardiovascular parameters others than Heart Rate, Blood Pressure and SpO2. The majority of pediatric measures are performed with cardiac ecographic metods and ultrasonography.

The NICaS device is based on cardiac impedenzometry measures: (ICG) there are two basical technologies developed;. Thoracic Body Bioimpedance (TEB) and Whole Body Electrical Bioimpedence (WBEB).

NICaS works in a different way to measure the cardiovascular parameters using the Whole Body Electrical Bioimpedence: the main difference compared to the adult's device consists in the number of electrodes and in their position on the little patient body.

Only two normal pediatric ECG electrodes are positioned in the left and the right wrist or in the ankle and the wrist.

An alternating electrical current at 30 Khz and 1,4 mA runs through the two electrodes and the delta in resistance (impedance) is measured; this is known as bioimpedance; the cardiac output is calculated during the time the strike volume passes from the left ventricle to the aorta (SV= Z/R).

During 2017 we applied a new mathematic algorithm dedicated to patients weighting less than 25 kg.

We compared the NICaS data in double check with a pediatric algorithm using a CardioQ ultrasonograph cardiac valutation device (CardioQ, Deltex medical;terminus RD, Chichester P019 8TX; United Kingdom).

We noticed that there was a good relation between the comparative data: these first results have been already presented.[11]

Soon after, we studied 41 neonatal and pediatric patients who had undergone cardiac surgery, urologic surgery, orthopedic surgery and general surgery, and we compared the two systems data: Cardiac Output. Heart Rate, Cardiac Index, Stroke Volume, Total Periferic Resistencies Index, Total body Wather, Cardiac Power Index.

The statistical and clinical were absolutely satisfactory and the algorithm has been validated.

There is already an article submitted for review[12] (Figures 6-8).

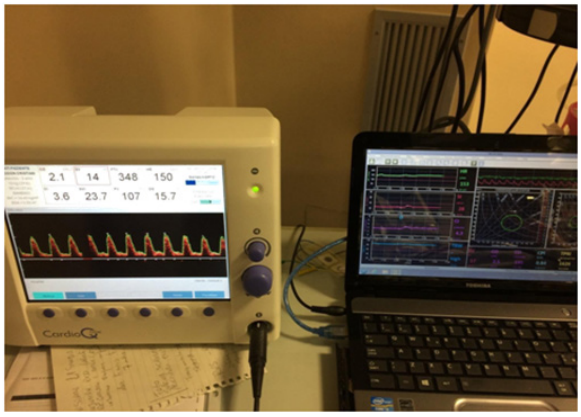

Figure 6 Non Invasive Cardiac System.

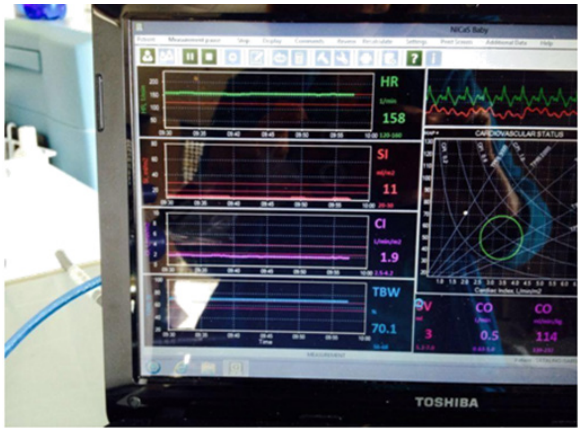

Figure 7 Non Invasive Cardiac System.

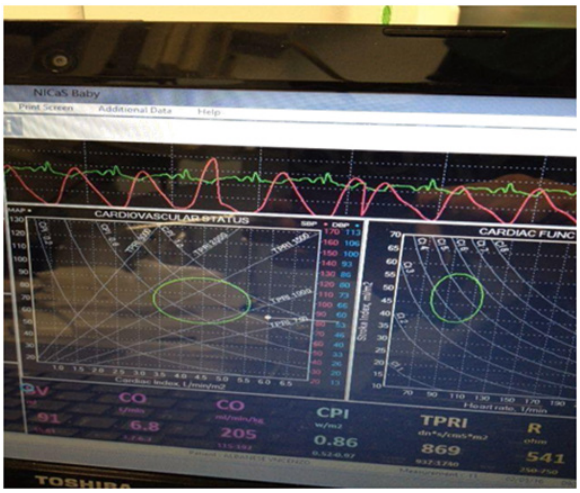

Figure 8 Non Invasive Cardiac System.

Neonatal and pediatric TCI (target controlled infusion)

TCI, acronimous for Target Controlled Infusion, identifies a computer driving an automatic anaesthesia system; it is a Glasgow-University Trade mark and is used especially in adults anesthesia. There are a few pharmacodinamic-pharmacokinetics programs dedicated to pediatric anesthesia. (Minto alfentanil PD-PK, Kataria Ketamine PD-PK); (Marsh-Kenny-White-Absalom-Lal-"Paedfusor").[13,14]

As we already said the aim of the device is to give anesthetists a better control over the use of anesthetic drugs and anesthesia plains established in advance.

Anaesthesia is performed using a combination of Theoretical dosages program algorithm validated by statistical and in vivo drug dosages.

The author's interest in pediatric TCI comes from middle 90s when he worked with Gavin NGC Kenny in Glasgow-UK and started to develop, define and apply pediatric PD-PK, from "0" weight patients using two TCI sperimental devices programmed with 12 theoretical PD-PK programs.[15]

The author's scientific activity continued in Italy with permission of CNR (National Agency for Research) in the following years.[16-19]

In April 2002 an article describing the author's study and research experience in TCI Pediatric Cardiac Anaesthesia was submitted for review to Minerva Anestesiologica,[20] but it was not reviewed and accepted for publication only October 2005 (Figure 9). Article never published; Data never published.

In the meanwhile Absalom and Kenny and Absalom and Lal, from Glasgow published the validation of a dedicate system for paediatric TCI named "Pedfusor" Glasgow University Registered.[13,14] The pediatric TCI didn't have no further active or adequate development.

Even nowadays it is very difficult to develop an accurate pediatric computer drive device due to many covariables.

In my opinion the difficulties in searching and validating a new GHEPTS PD-PK Thricompartimental Model derives from the fact that we cannot compare and use the adult PD-PK pharmacological criteria to control the changes and the activity of a drug in neonate and toddlers up to 30 kg of weight when a bolus followed by continuous infusion is started.

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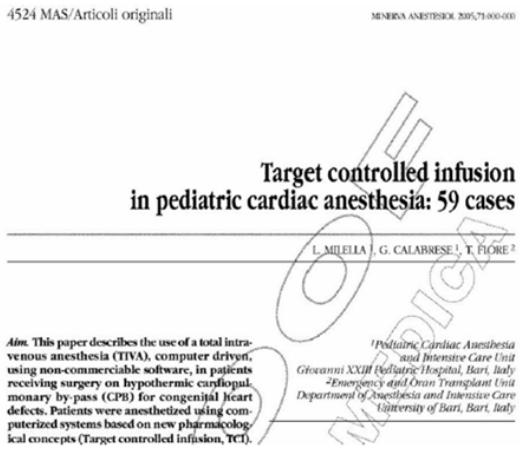

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Target controlled infusion in pediatric cardiac anesthesia: 59 cases

L. MILELLA [1], G. CALABRESE [1], T. FIORE [2]

Aim. This paper describes the use of a total intravenous anesthesia (TIVA), computer driven, using non-commerciable software, in patients receiving surgery on hypothermic cardiopulmonary by-pass (CPB) for congenital heart defects. Patients were anesthetized using computerized systems based on new pharmacological concepts (Target controlled infusion, TCI).

[1] Pediatric Cardiac Anesthesia and Intensive Care Unit Giovanni XXIII Pediatric Hospital, Bari, Italy; [2] Emergency and Oran Transplant Unit Department of Anesthesia and Intensive Care University of Bari, Bari, Italy

Figure 9 Target controlled infusion.

In other words the PD-PK pharmacological concepts are not enough. In the last two years the author started to develop a new algorithm to build up a new pharmacological Theoretical Third Compartment at equilibrium using different PD-PK concepts derivated from the study of the laws regulating the fast growth cells characteristic.

The aim of the study and research is to develop a device that takes in account all the covariables derivating from the non linear relationship between Metabolic Power/Body Mass Index.

A first lecture about the author work has already been presented[21] and an article is on the way to be submitted for review.

Conclusion

This brief report wants to describe the daily activity of a multidisciplinary ICU that takes care of patients ranging from first day of birth (and as regards cardiac surgery even in premature neonates) to 16 years of age.

Many of the data presented and part of the discussion is short in argumentations because articles are on the way of review, to be submitted and or near to be published and legal reasons oblige the author not to give specific information's.

But our strong intention was to give a picture of the activity of a dedicated neonatal and pediatric unit acting in a Third Level Pediatric Hospital in South of Italy.

Acknowledgments

None.

Conflicts of interest

None.

Funding

None.

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