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PCO2 gap - As an Endpoint of Resuscitation and Predictor of Mortality in Patients with Shock: A Prospective Observational Study

By Dr. Prabhu S, Dr. Vimal Bhardwaj, Dr. V. Viju Wilben & Mr. Vinil Kumar

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Aim: To evaluate the association between PCO2 gap and outcome of resuscitation in patients with shock. The Objectives of the project are to study the association between PCO2 difference and in-hospital mortality in patients admitted with shock and to study the correlation between PCO2 difference and lactate clearance.

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PCO2 gap – As an Endpoint of Resuscitation and Predictor of Mortality in Patients with Shock: A Prospective Observational Study

Dr. Prabhu S [α], Dr. Vimal Bhardwaj [σ], Dr. V. Viju Wilben [ρ] & Mr. Vinil Kumar [ω]

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Materials and methods: 71 adult patients presenting with shock to our ER were enrolled in the study. They were resuscitated according to standard protocols. PCO2 gap was measured at presentation, then every 2 hours until the resolution of shock which were correlated to the lactate clearance, hemodynamics and the IVC index of the patient. The data was then analyzed using the R software and logistic regression was done to analyze various factors associated with mortality. P value less than 0.05 was considered statistically significant.

Results: The correlation between pCO2 gap and the in hospital mortality was statistically significant at 0,2,4,6 and 24 hours. The correlation between pCO2 gap and the end point of resuscitation was statistically significant at 2,4,6 and 24 hours implied by the pearson's correlation. We also found a positive correlation between PCO2 gap and lactate clearance which was statistically significant.

Conclusion: The PCO2 gap can be used a marker of the adequacy of the cardiac output in patients with shock. Using pCO2 gap has potential to avoid administration of unnecessary fluids and inotropes in patients, who have lactate elevated in the absence of tissue hypo perfusion. We suggest using pCO2 gap as a complementary tool to evaluate the adequacy of blood flow to global metabolic demand. A high pCO2 gap on initial presentation was associated with high mortality rates. So it can be used as a predictor of outcomes in patients with shock.

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I. Introduction

Shock is the clinical expression of circulatory failure that results in inadequate cellular oxygen utilization.[1] Shock is a common condition in critical care, affecting about one third of patients in the intensive care unit (ICU), both over resuscitation and under resuscitation can adversely impact the outcomes.[2,3,4] End point of resuscitation has always been a matter of debate, initially continuous SCvo2 monitoring as introduced by Rivers et al had the obvious limitation that normal/high values cannot discriminate whether delivery is adequate or in excess to demand[5,6,7]. High ScvO2 profiles have even been shown to be related to elevated blood lactate concentration and poor survival rates.[8]

Lactate cannot differentiate between different etiologies of shock and it can get elevated in various other conditions.[9] Carbon dioxide (Co2) is highly diffusible and can be a marker of adequacy of venous return, the central venous and arterial CO2 gap, as an easily available clinical monitoring tool. Observational study has shown that Persistence of such a large pCO2 gap after 24 hours of treatment was predictive of higher mortality.[10]

In conclusion, determining the PCo2 gap during resuscitation of critically ill patients is useful in deciding when to stop resuscitation.[11] Central venous-arterial carbon dioxide difference (PCO2 gap) can be a marker of cardiac output adequacy in global metabolic conditions that are less affected by the impairment of oxygen extraction capacity. Assessing the adequacy of oxygen delivery with oxygen requirements is one of the key-goal of hemodynamic resuscitation. Clinical examination, lactate and central or mixed venous oxygen saturation (SvO2 and ScvO2, respectively) all have their limitations. Many of them may be overcome by the use of the carbon dioxide (CO2)-derived variables. The venoarterial difference in CO2 tension ("ΔPCO2" or "PCO2 gap") is not an indicator of anaerobic metabolism since it is influenced by the oxygen consumption. By contrast, it reliably indicates whether blood flow is sufficient to carry CO2 from the peripheral tissue to the lungs in view of its clearance: it, thus, reflects the adequacy of cardiac output with the metabolic condition. We investigate the relation between

the PCO2 gap and serum lactate and its role in resuscitation of patients with septic shock.

II. Review of Literature

Shock is defined as inability to maintain MAP which is refractory to fluid resuscitation. It has a guarded prognosis, there are many upstream and downstream markers for resuscitation, septic shock guidelines endorses Lactate as a prognostic marker; has got its own limitations as it can be elevated in other clinical conditions9 and it cannot differentiate the cause of shock9. With enough evidence coming up about over resuscitation and positive balance being one of the predictor of mortality there is a need for ideal resuscitation marker which can be easily employed bedside with present day equipment used on day to day basis.

CO2 is the end product of aerobic metabolism, PCO2 in the venous blood reflects the global tissue blood flow relative to metabolic demand. CO2 is about 20 times more soluble than O2 so it more reliably diffuses out of ischemic tissues into the venous effluent making it a sensitive marker of hypoperfusion in situations where an O2 diffusion barrier exists (e.g. non-functional and obliterated capillaries), "masking" poor O2 extraction (O2ER) and increased tissue O2 debt, CO2 still diffuses to the venous effluent, "unmasking" the low perfusion state for the clinician when venous-to-arterial CO2 difference is evaluated the gap is a marker of adequacy of venous blood flow to remove CO2 produced rather than a marker of tissue hypoxia or dysoxia[11]

Table 1: PCO2 Gap in Different Shock States

Shock type	Lactate	O2ER	ScvO2	cvaCO2gap
Cardiogenic or hypovolemic	HIGH	HIGH	LOW	HIGH
Anemic or hypoxemic	HIGH	HIGH	LOW	LOW
Distributive	HIGH	LOW	HIGH	HIGH
Cytopathic	HIGH	LOW	HIGH	LOW

As illustrated in table 1, Lactate is high in all types of shock, PCO2 Gap is high in cardiogenic and distributive shock which is amenable to fluid resuscitation and inotropic support and low in hypoxemic and cytopathic shock where fluid resuscitation has no role thus it can be concluded that PCO2 gap is useful in determining when to start and stop fluid resuscitation.[11] Co2 gap is a marker of adequacy of venous blood rather than marker of tissue hypoxia or dysoxia as shown by Vallet et al in an experimental model of isolated limb in which ischemic hypoxia (IH) and hypoxic hypoxia (HH). The authors demonstrated that when DO2 was reduced beyond its critical threshold in IH (dysoxia), this was associated with an increased limb venous-to-arterial PCO2gap.[12]

Conversely, in HH, pCO2 gap did not increase in spite of a marked VO2 and VCO2 reduction.[12] There is a good correlation between Mixed CO2 and Central CO2 difference with Arterial CO2 as demonstrated by Van Beest et al in severe sepsis and septic shock patients, hence Central CO2 can be substituted for mixed CO2 for determining the CO2 gap which acts as surrogate marker for Cardiac Index.[10]

Cushieri J etal conducted study in ICU patients to see the correlation between Central Venous and Arterial CO2 gap and Cardiac index determined by thermodilution technique and showed statistically significant correlation.[13]

Hence CO2 gap can be used as a marker of Cardiac output.

a) Role in Sepsis

In sepsis although Cardiac output may be normal but regional compromise of circulation is well documented phenomenon which may lead to increase in CO2 secondary to micro-circulation compromise. P(cv-a)CO2 could be considered as a better indirect assessment of systemic blood flow than ScvO2 in resuscitated-septic shock patients.[14]

A cutoff value for pCO2 gap of 0.8 kPa (6mmHg) discriminated between high and low lactate clearance and CI.[15,16] In study done by Vallee et al done in septic shock patients compared When the 70% ScvO2 goal value is reached, the presence of a P(cv-a)CO2 larger than 6 mmHg shown to be an useful tool to identify patients who still remain inadequately resuscitated.[14]

We hypothesize that CO2 gap is non inferior to lactate clearance in resuscitation of critically ill patients.

III. Research Question

Would pCO2 gap serve as an ideal bedside marker to predict the outcome of resuscitation in a patient with shock?

IV. Aims and Objectives

Aim of the Project: To study the association between PCO2 gap and outcome of resuscitation in patients with shock.

Objectives of the Project: The Objectives of the project are as follows:

- Primary objectives- To study the association between PCO2 gap and in-hospital mortality in patients admitted with shock.
- Secondary objectives

➢ To study the correlation between PCO2 gap and lactate clearance.

➢ To study the role of PCO2 gap as a marker for endpoint of resuscitation in patients with shock.

V. Methods and Methodology

Study area: Emergency Department and medical intensive care unit, NH Health City, Bangalore

Study population:

- Inclusion Criteria

– All adult patients (more than 18 years of age) in shock requiring vasopressor to maintain MAP of 65mmHg, having a central venous access and arterial line.

- Exclusion Criteria

– Patient Refusal
– Pregnancy
– Advance directive with consensus against active resuscitation
– Disseminated Malignancy

Sample size: 71

Study design: Prospective observational study.

Study intervention: No interventions

Study duration: One Year

VI. Methodology

✧ All shock patients were resuscitated according to the standard protocol with fluid bolus of 30 ml/kg over 1 hour and guided therapy with fluid challenges targeting heart rate, base deficit, urine output and pulmonary congestion as per routine clinical practice.

✧ Lactate clearance was documented every 2nd hourly and VBG from Central line and ABG from Radial Line was analyzed at the same time and CO2 gap was checked every 2nd hourly.

✧ Screening 2D-echocardiography was done at the emergency department and inotropic agent was decided based on heart contractility.

✧ Patient demographic details, diagnosis, SOFA Score, was done in the first 6 hours of resuscitation (two hours apart) and the data was collected. Lactate and Co2 Gap were captured and documented after 24 hours of resuscitation.

✧ Aim of resuscitation was to target MAP of 65 mm Hg and two stable lactate values 2 hours apart. If lactates had not improved then further fluid boluses were decided upon reviewing pulmonary congestion in ultrasound (M mode of lung will be done and if B lines are more than 4 then it is indicative of pulmonary congestion). The corresponding CO2 Gap was noted.

✧ First choice of vasopressor was nor-adrenaline as per the standard infusion dose. If patient requires vasopressor support despite fluid boluses then steroid in the form of injection Hydrocortisone 50mg IV every 6th hourly was administered.

✧ Antimicrobial administration and further management was decided by clinical examination and supportive investigations as per clinician's judgement.

Data collection methods: Proforma

Data collection forms: Attached

VII. Statistical Methods

a) Sample Size Calculation

Sample size was calculated using nMaster software v2.0

In a study done by Beest PV et al, the mortality of patients with sepsis was 24.5% (13 out of 53) and risk of mortality for those with high PCO2 gap ranged from 1.6 to 5.3

Keeping a conservative value in odds ratio as 2.5, with power of 80% and 5% alpha error the minimum required sample size is 71.

b) Statistical Analysis Plan

Data was analyzed using R software. Continuous variable were described using mean and standard deviation. Categorical variables were described using frequency and percentage. Patients were categorized based on PCO2 difference and logistic regression was done to analyze various factors associated with mortality. Correlation between PCO2 difference and lactate was done using appropriate statistical methods. P value less than 0.05 was considered statistically significant.

c) Ethical consideration

Ethical clearance was obtained prior to the study from the ethics committee of the institution. Informed consent was obtained from the patient or guardian before the onset of study. Confidentiality of

patient details are and will be maintained. It was explained to the patient that the study is purely descriptive and merely for data collection. There is no intervention required specifically for the study. Management of these patients were along the standard international guidelines. As the study did not involve any extra procedure, no compensation was offered during and after the study.

VIII. Results

A total of 71 patients were enrolled in the study. 7 patients died from the 48 to 72 hours time period. Their samples were collected and analyzed till the 24th hour of admission. The mean age of the patients was 54 years (SD 16.2; range 18–81 years).

Table 2: Demographic and disease characteristics

Variable					
Age	Median 57	Mean 54	SD 16.2	Minimum 18	Maximum 81
Gender	Male - 24 Female- 47				
SOFA score at enrollment		Mean 9		Minimum 2	Maximum 19
Type of shock	Frequency				
Anemic	1				
Cardiogenic	14				
Distributive	50				
Hypovolemic	3				
Hypoxemic	2				
Neurogenic	1				
Fluid requirement In ml	Median 2000	Mean 2076	SD 998	Minimum 500	Maximum 4500

The primary outcome of the study was the correlation between the PCO2 gap and the in hospital mortality at each of the sampling time points. The correlation between the PCO2 gap and the in hospital mortality was positive at 0, 2, 4, 6 and 24hours. The correlation was statistically significant at 0 and 2 hours. (Table 2)

Table 3: Correlation between the PCO2 gap and the in hospital mortality

Time point	Point biserial correlation (rpb)	Probability (p) value
0 hour	0.309	0.009
2 hours	0.358	0.002
4 hours	0.200	0.108
6 hours	0.096	0.473
24 hours	0.170	0.207

There was a statistically significant negative correlation between end point of resuscitation and pCO2 gap at 2h,4h, 6h and 24 hours as implied by the Pearson's correlation in Table 3.

Table 4: Correlation between the PCO2 gap and end point of resuscitation

Time Point	Point Biserial Correlation (Rpb)	Probability (P) Value
0 hour	-0.206	0.121
2 hours	-0.206	0.011
4 hours	-0.350	0.010
6 hours	-0.380	0.007
24 hours	-0.398	0.007

It was also observed that the pco2 gap at 0h,2h,4h, 6hours had a statistically significant positive correlation with lactate clearance.(Table 4)

Table 5: Correlation between the PCO2 gap and lactate clearance

Time point	Point biserial correlation (rpb)	Probability (p) value
0 hour	0.390	0.001
2 hours	0.362	0.002
4 hours	0.318	0.009
6 hours	0.311	0.018
24 hours	0.311	0.068

IX. Discussion

The association of lactate accumulation and oxygen debt during shock states has been described for decades15. Throughout the years, there has been continued interest in refining resuscitation triggers, and response to therapy. Lactate clearance as an endpoint of resuscitation is supported by at least two multi-center studie[16,17]. However, lactate clearance has disadvantages as lactates can sometimes be normal in septic shock[18], lactate elevation not solely due to oxygen delivery- consumption mismatch and it has different prognostic implications based on the initial value.

It was recognized in sepsis that pCO2 gap (or its mathematical derivatives) outperformed other markers in detecting tissue hypoperfusion[13,19-21]. The arterial carbon dioxide is dependent on the pulmonary gas exchange and the venous carbon dioxide is dependent on the blood flow to the tissue[22]. So, when the flow reduces in low cardiac output states like shock, the difference between the venous and arterial carbon dioxide increases. It has been demonstrated that the pCO2 gap increases in various types of shock.[2]

In our study we found a statistically significant correlation of pCO2 gap at 0 hour and and 2nd hour of resuscitation and mortality in patients. It shows that high pCO2 gap on initial presentation can be used as a predictor of outcomes in patients with shock. Ospina-Tascón, G.A. et al.,[24] found that the persistence of high PCO2gap during the early resuscitation of septic shock was associated with higher 28 day mortality.

We also found that there was a statistically significant correlation between end point of resuscitation and pCO2 gap at 2h,4h, 6h and 24 hours. Hence, pco2 gap can be used as an endpoint of resuscitation in patients with shock. This was similar to the findings of Vallet B et al.,[11] who found that determining the gap during resuscitation of critically ill patients is useful when deciding when to stop resuscitation.

Our analysis also showed that PCO2 gap at various time points had positive correlation with lactate clearance. This was similar to a study done by Shyam M et al.,[25] who showed that the PcvCO2–PaCO2/CaO2–CcvO2 ratio and lactate are positively correlated during the first 24 hours of active resuscitation from sepsis-induced hypotension,

Pco2 gap is not inferior to lactate levels as a hemodynamic marker. It can be substituted in place of lactate levels to predict outcomes in patients presenting with shock. It can also be used as a guide for therapy to achieve endpoint of resuscitation.

X. Limitations

Our study has its limitations. It is a descriptive study without randomization of the patients. Also some technical aspects should be kept in mind when these indices are used in clinical practice. First, some errors in the PCO2 gap measurements may occur when sampling the venous blood: incorrect sample container, contaminated sample by air or venous blood or catheter fluid. Second, a too long delay of transport of blood sampling may significantly change the blood gas content at the venous and the arterial site.

XI. Summary and Conclusion

The PCO2 gap can be used a marker of the adequacy of the cardiac output in patients with shock. Using pCO2 gap has potential to avoid administration of unnecessary fluids and inotropes in patients, who have lactate elevated in the absence of tissue hypo perfusion. We suggest using pCO2 gap as a complementary tool to evaluate the adequacy of blood flow to global metabolic demand. A high pCO2 gap on initial presentation was associated with high mortality rates. So it can be used as a predictor of outcomes in patients with shock.

List of abbreviations

ICU - Intensive care unit

MAP- Mean arterial pressure

CO2- carbon dioxide

PCO2- Partial pressure of carbon dioxide

EtCO2- End tidal concentration of carbon dioxide

CVP- Central venous pressure

SCVO2- Central venous oxygen saturation

VO2- Oxygen consumption

VCO2- Carbon dioxide output

CaCO2- Carbon dioxide content in the blood

K pa- Kilo pascal

SOFA- Sequential organ failure assessment

Mm Hg- millimeters of mercury.

VBG- Venous blood gas

ABG- Arterial blood gas.

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Appendices

Proforma

PCO2 Gap – AS AN ENDPOINT OF RESUSCITATION AND PREDICTOR OF MORTALITY IN PATIENTS WITH SHOCK.

1. DATE OF ADMISSION :
2. AGE : ___ YEARS
3. SEX : MALE / FEMALE
4. COMORBIDITIES : DIABETES / HYPERTENSION/ IHD/ CKD/THYROID DISORDERS/ OTHERS __
5. PROVISIONAL DIAGNOSIS :
6. TYPE OF SHOCK : CARDIOGENIC/HYPOVOLEMIC/DISTRIBUTIVE/ANEMIC OR HYPOXEMIC/CYTOPATHIC
7. SOFA SCORE :
8. MEAN ARTERIAL PRESSURE (ON ARRIVAL TO ER) :
9. FLUID BOLUS : YES/ NO
   SPECIFY DETAILS –
10. VASOPRESSOR : YES/ NO, if YES specify the drug _____
11. DOBUTAMINE SUPPORT : YES/ NO
12. ENDPOINT OF RESUSCITATION:
13. FINAL OUTCOME OF PATIENT :

TIME	LACTATE mmol/L	P(cv-a)CO2 mmHg	SCVO 2 %	END POINT OF RESUSCITATION		
				MAP	IVC COLLAPSIBILITY	PULMONARY EDEMA
ARRIVAL						
2 HOURS						
4 HOURS						
6 HOURS						
24 HOURS						

Informed Consent and patient information sheet

Dr. Prabhu,
Emergency medicine department,
Narayana health.

This Informed Consent Form is for men and women who come to the emergency department in state of shock- with low blood pressure not responding to IV fluids, and who we are inviting to participate in research. The title of our research project is PCO2 Gap – AS AN ENDPOINT OF RESUSCITATION AND PREDICTOR OF MORTALITY IN PATIENTS WITH SHOCK: A PROSPECTIVE OBSERVATIONAL STUDY.

This Informed Consent Form has two parts:
Information Sheet (to share information about the research with you)
Certificate of Consent (for signatures if you agree to take part)

PART I: Information Sheet

Introduction

I am Dr. Prabhu. We are doing research on patients presenting with shock to the emergency room, which can occur due to various causes like blood loss, cardiac failure, infection, anemia. I am going to give you information and invite

you to be part of this research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, or the staff.

pCO2 gap is the difference between the venous and arterial carbon dioxide. When a patient presents with shock, they will be treated with IV fluids or medication to increase blood pressure (inotropes) by constriction of blood vessels depending upon the cause of the shock. To know when the shock has resolved, we are going to compare pCO2 gap to other parameters which have been previously established.

Purpose of the research

To evaluate if pCO2 gap can be used to predict mortality and marker for end point of resuscitation

Participant selection

We are inviting all adults with shock to participate in the research on pCO2 gap.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at the hospital will continue and nothing will change. You may change your mind later and stop participating even if you agreed earlier.

Procedures and Protocol

Once you understand the study and give consent, your pCO2 gap will be measured on presentation, 2nd hour, 4th hour, 6th hour and at 24th hour. Patients presenting with shock will have an arterial line for invasive blood pressure measurement and a central line for administration of inotropes to treat the shock. Blood samples from these lines will help us to measure pCO2 gap. Treatment will be given for the shock as per standard guidelines and hospital protocol according to the patient's condition. Other parameters such as mean arterial pressure, IVC collapsibility, lactates will be compared to find out if pCO2 gap has a good correlation for endpoint of resuscitation (resolution of shock)

Duration

The research takes place over the course of 1 year. You will be followed up for12 to 24 hours depending upon your clinical condition.

Side Effects

No new intervention or procedure is done for the study. You will already have lines from which blood samples will be taken. Hence there are no side effects for the study.

Risks

No additional risks and discomfort will be caused during this study.

Benefits

The findings of this study can change the views of using pCO2 gap as an endpoint of resuscitation.

Confidentiality

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this hospital in any way. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this hospital will not be affected in any way.

Whom to contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

Contact the principal investigator
Name: Dr. Prabhu
Address: Narayana Health City, Bangalore
Contact No. 7358248887
Email: prabhu.adms@gmail.com

This proposal has been reviewed and approved by Narayana Health Academic ethical committee, which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the IRB, contact Narayana Health Academic Ethics Committee. Name: Dr. Sanjay Rao
Designation: Member Secretary
Contact No. 9538008940;
Email: nhaec@narayanahealth.org

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____
Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the objectives of the research.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____ Day/month/year

Print name of the impartial witness in capitals_____

Signature of impartial witness_____

Date _____ Day/month/year

Deferred Consent for Research Participation

Title of Project: PCO2 Gap – AS AN ENDPOINT OF RESUSCITATION AND PREDICTOR OF MORTALITY IN PATIENTS WITH SHOCK: A PROSPECTIVE OBSERVATIONAL STUDY.

Principal Investigator: Dr. Prabhu
Emergency medicine department,
Narayana health,Phone Number: 7358248887

The patient named below is being enrolled in this research study by deferred consent. The process of obtaining written informed consent will be deferred until after the patient is able to understand and has capacity to give consent. Written informed consent will be obtained to continue data collection after resuscitation from the patient or, if the patient lacked capacity, a legal representative.

Patient's Name: _____

Date/time assessed for enrolment: _____/_____/_____ (dd/mm/yyyy) at ____ : _____ (time)

Reason(s) deferred consent process is used (check all that apply):

____ The patient is unconscious or lacks capacity to understand the risks, methods and purposes of the research study.

____ No next of kin/substitute decision maker is available to provide consent, or attempts to contact them have been unsuccessful despite diligent and documented efforts.

____ A substitute decision maker _____ (name and relationship) has been contacted by telephone, and the purpose, methods and risks of participation in this study have been explained to the third party. While the substitute decision maker has given verbal consent for participation, written consent must be still be obtained.

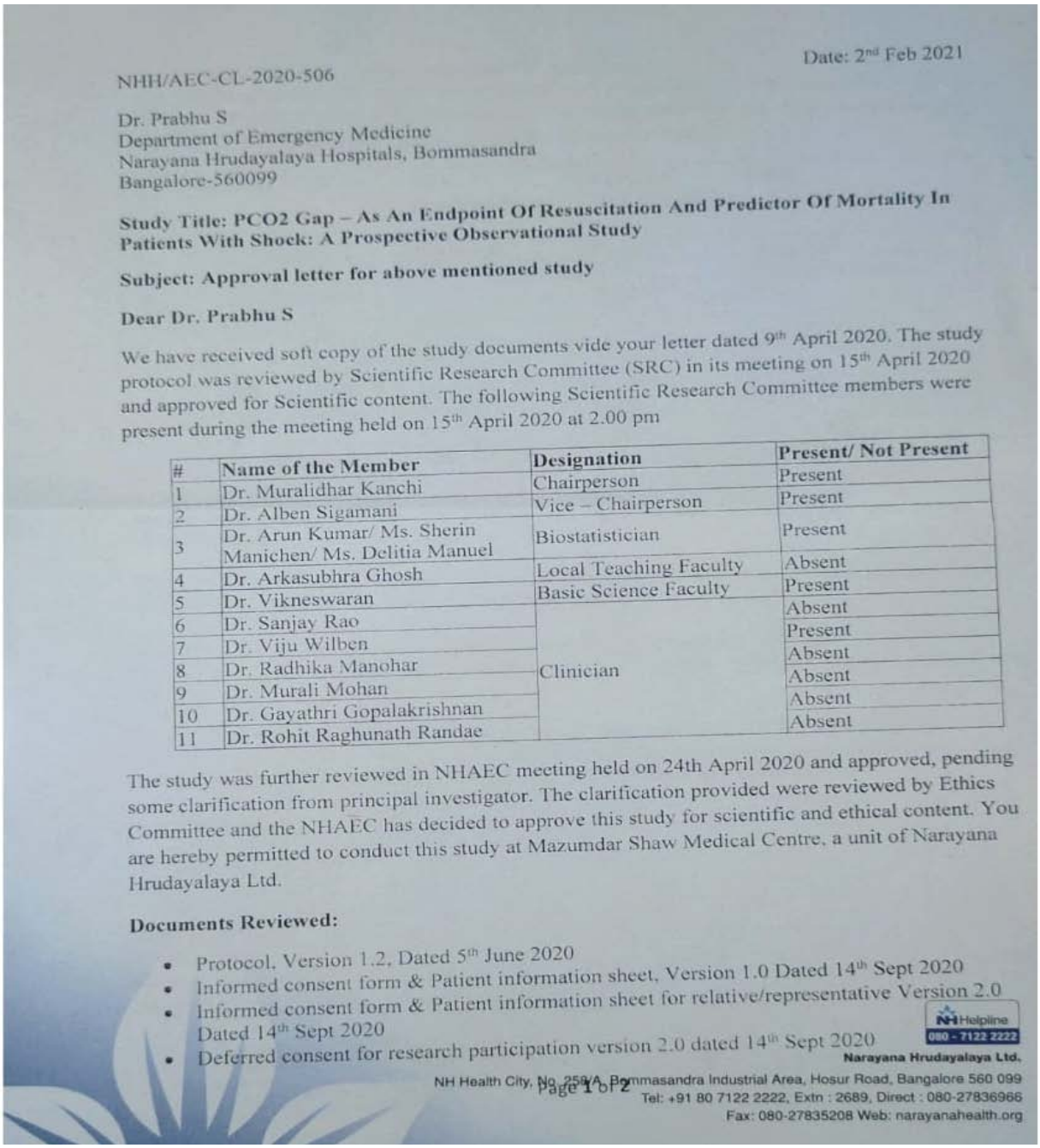
____ No relevant prior directive by the patient is known to exist.

____ Other: _____

_____ _____

Signature of investigator Date and Time

Annexure 1



Date: 2nd Feb 2021

NHH/AEC-CL-2020-506

Dr. Prabhu S
Department of Emergency Medicine
Narayana Hrudayalaya Hospitals, Bommasandra
Bangalore-560099

Study Title: PCO2 Gap – As An Endpoint Of Resuscitation And Predictor Of Mortality In Patients With Shock: A Prospective Observational Study

Subject: Approval letter for above mentioned study

Dear Dr. Prabhu S

We have received soft copy of the study documents vide your letter dated 9th April 2020. The study protocol was reviewed by Scientific Research Committee (SRC) in its meeting on 15th April 2020 and approved for Scientific content. The following Scientific Research Committee members were present during the meeting held on 15th April 2020 at 2.00 pm

#	Name of the Member	Designation	Present/ Not Present
1	Dr. Muralidhar Kanchi	Chairperson	Present
2	Dr. Alben Sigamani	Vice – Chairperson	Present
3	Dr. Arun Kumar/ Ms. Sherin Manichen/ Ms. Delitia Manuel	Biostatistician	Present
4	Dr. Arkasubhra Ghosh	Local Teaching Faculty	Absent
5	Dr. Vikneswaran	Basic Science Faculty	Present
6	Dr. Sanjay Rao	Clinician	Absent
7	Dr. Viju Wilben		Present
8	Dr. Radhika Manohar		Absent
9	Dr. Murali Mohan		Absent
10	Dr. Gayathri Gopalakrishnan		Absent
11	Dr. Rohit Raghunath Randae		Absent

The study was further reviewed in NHAEC meeting held on 24th April 2020 and approved, pending some clarification from principal investigator. The clarification provided were reviewed by Ethics Committee and the NHAEC has decided to approve this study for scientific and ethical content. You are hereby permitted to conduct this study at Mazumdar Shaw Medical Centre, a unit of Narayana Hrudayalaya Ltd.

Documents Reviewed:

- Protocol, Version 1.2, Dated 5th June 2020
- Informed consent form & Patient information sheet, Version 1.0 Dated 14th Sept 2020
- Informed consent form & Patient information sheet for relative/representative Version 2.0 Dated 14th Sept 2020
- Deferred consent for research participation version 2.0 dated 14th Sept 2020

NH Helpline 080 - 7122 2222

Narayana Hrudayalaya Ltd.
NH Health City, No. 258/A, Bommasandra Industrial Area, Hosur Road, Bangalore 560 099
Tel: +91 80 7122 2222, Extn : 2689, Direct : 080-27836966
Fax: 080-27835208 Web: narayanahealth.org

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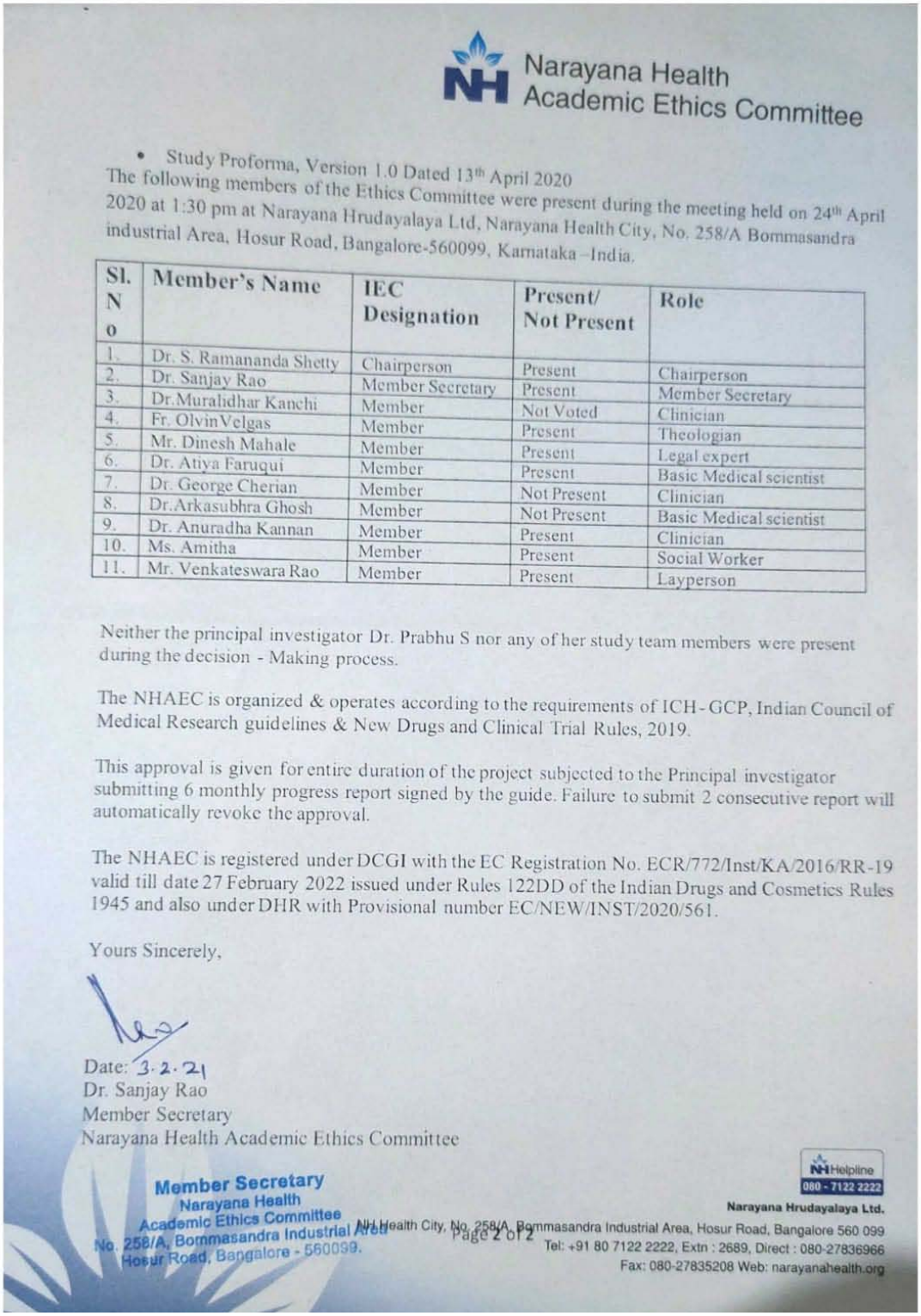
Annexure ii



Narayana Health
Academic Ethics Committee

- Study Proforma, Version 1.0 Dated 13th April 2020

The following members of the Ethics Committee were present during the meeting held on 24th April 2020 at 1:30 pm at Narayana Hrudayalaya Ltd, Narayana Health City, No. 258/A Bommasandra industrial Area, Hosur Road, Bangalore-560099, Karnataka –India.

Sl. No	Member's Name	IEC Designation	Present/ Not Present	Role
1.	Dr. S. Ramananda Shetty	Chairperson	Present	Chairperson
2.	Dr. Sanjay Rao	Member Secretary	Present	Member Secretary
3.	Dr.Muralidhar Kanchi	Member	Not Voted	Clinician
4.	Fr. Olvin Velgas	Member	Present	Theologian
5.	Mr. Dinesh Mahale	Member	Present	Legal expert
6.	Dr. Atiya Faruqui	Member	Present	Basic Medical scientist
7.	Dr. George Cherian	Member	Not Present	Clinician
8.	Dr.Arkasubhra Ghosh	Member	Not Present	Basic Medical scientist
9.	Dr. Anuradha Kannan	Member	Present	Clinician
10.	Ms. Amitha	Member	Present	Social Worker
11.	Mr. Venkateswara Rao	Member	Present	Layperson

Neither the principal investigator Dr. Prabhu S nor any of her study team members were present during the decision - Making process.

The NHAEC is organized & operates according to the requirements of ICH-GCP, Indian Council of Medical Research guidelines & New Drugs and Clinical Trial Rules, 2019.

This approval is given for entire duration of the project subjected to the Principal investigator submitting 6 monthly progress report signed by the guide. Failure to submit 2 consecutive report will automatically revoke the approval.

The NHAEC is registered under DCGI with the EC Registration No. ECR/772/Inst/KA/2016/RR-19 valid till date 27 February 2022 issued under Rules 122DD of the Indian Drugs and Cosmetics Rules 1945 and also under DHR with Provisional number EC/NEW/INST/2020/561.

Yours Sincerely,

Date: 3.2.21
Dr. Sanjay Rao
Member Secretary
Narayana Health Academic Ethics Committee

Member Secretary
Narayana Health
Academic Ethics Committee
No. 258/A, Bommasandra Industrial Area
Hosur Road, Bangalore - 560099.

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