Original Article

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Monitoring Microcirculatory Blood Flow during Cardiopulmonary Bypass in Paediatric Cardiac Surgery Patients as a Predictor for Anaerobic Metabolism

RAMESH PATEL[1], ATUL SOLANKI[2], HASMUKH PATEL[3], JIGNESH PATEL[4], HIMANI PANDYA[5], JAINAM SHARMA[6]

ABSTRACT

Introduction: Improving tissue oxygenation is one of most important tasks in management of low cardiac output. Central venous oxygen saturation ($ScvO_2$) and lactate are established criteria for monitoring the adequacy of tissue oxygenation. The venous-to-arterial carbon dioxide difference [$P(v\text{-}a)CO_2$] is inversely associated with cardiac output.

Aim: To study the use of $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio as a marker of low cardiac output during Cardiopulmonary Bypass (CPB) in paediatric cardiac surgical patients.

Materials and Methods: The present study was a prospective observational study conducted over a period of nine months from 1st August 2015 to 30th April 2016. A total of 110 children were enrolled, who underwent CPB during cardiac surgery. The CPB time, Mean Arterial Pressure (MAP), flow rate, cross clamp time, were recorded for all the patients as well as Arterial Blood Gas (ABG) and Venous Blood Gas (VBG) were checked at four different points of time: 1) Before CPB, 2) 10 minutes after initiation of CPB, 3) 30 minutes on CPB and 4) off CPB.

Results: The results indicated that Receiver Operating Characteristic curve (ROC curve) at 30 minute of CPB time $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ was more specific and sensitive than lactate to detect anaerobic metabolism. Decrease platelet count was significant on second postoperative day.

Conclusion: The present study suggests the use of $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio as a marker to detect low flow on CPB. Our study was single centric and with a small size, studies involving large population and multiple centers are required to support the recent findings.

Keywords: Arterial blood gas, Central venous oxygen saturation, Venous blood gas

INTRODUCTION

Tissue hypoxia due to low cardiac output or CPB induced inflammatory response is an important predictor of multiorgan failure [1]. Systemic blood pressure and ratio of oxygen demand versus supply are commonly used techniques for monitoring tissue oxygenation [2]. Early Goal Directed Therapy (GDT) that includes targeted haemodynamic parameters, mix venous oxygen saturation and lactate level improves patient outcome in septic shock as well as in severe sepsis [3]. Multiorgan dysfunction resulting in death, has been reported in a number of patients inspite of maintaining systemic haemodynamic parameters and mixed venous saturation [4,5].

Shock such as cardiogenic, septic, hypovolemic or obstructive aetiology leads to decrease in tissue perfusion, which reflects as increase in $P(v\text{-}a)CO_2$ on blood gas analysis [5-7].

An inverse relationship between $P(v\text{-}a)CO_2$ and cardiac output has been described. Even after achieving haemodynamic and mix venous oxygen saturation targets, a persistently high $P(v\text{-}a)CO_2$ indicates inadequate resuscitation in septic patients [8]. Thus, $P(v\text{-}a)CO_2$ is an important marker to track global tissue perfusion and early detection of rise in CO_2 due to anaerobic metabolism [9].

Recent studies have tried to demonstrate the reliability of $P(v\text{-}a)CO_2$ as a tool in resuscitation of septic patients [10]. The haemodynamic management of patients in shock aims at improving tissue oxygenation. $ScvO_2$ is a useful tool reflecting the global transport and metabolism of oxygen. Persistently low $ScvO_2$ indicates inadequate tissue perfusion leading to tissue hypoxia and is associated with increase in postoperative morbidity [11-13].

Low $ScvO_2$ along with increase in postoperative complications has been observed in a recent study on individualized goal directed therapy [14]. A high $ScvO_2$ value may not reflect adequacy of microcirculation, limiting its use in routine clinical practice [15,16].

Interestingly, central venous-to-arterial PCO_2, differences $P(v\text{-}a)CO_2$, with central venous PCO_2 as a surrogate for mixed venous PCO_2 has recently been proposed as a useful tool for GDT in ICU-septic patients to identify persistent hypoperfusion when a $ScvO_2 > 70\%$ has been reached [17]. Decreased tissue blood flow (ischemic hypoxia) represents the major determinant of increased $P(v\text{-}a)CO_2$[18], and $P(v\text{-}a)CO_2$ could therefore be considered as an indicator of adequate venous blood flow to remove CO_2 produced by peripheral tissues [19,20]. Lactate clearance, measured at a particular time interval, also assesses tissue oxygen delivery [21].

MATERIALS AND METHODS

This prospective observational study was carried out after approval by Institutional Ethics Committee and written and informed consents were obtained for all patients/parents who participated in the study. The time period was 1st August 2015 to 30th April 2016, and conducted at UN Mehta Institute of Cardiology and Research Centre, Ahmedabad, Gujarat, India. A total of 110 children, who underwent CPB during cardiac surgery, were included. Exclusion criteria were age more than 18 years, emergency surgery and refusal to participate in study.

Preoperative variables including demographics, diagnosis and previous medical history were collected. Intraoperative variables like CPB time, MAP, flow rate, cross clamp time, were recorded for all the patients. ABG and VBG were checked at four points: 1) Before CPB; 2) 10 minutes; 3) 30 minutes after initiation of CPB; and 4) off CPB.

Postoperative vitals, urine output, ABG, VBG, CBC, serum lactate, Chest X-ray (CXR) and Renal Function Test (RFT) were collected for 72 hours.

We measured oxygen tension, saturation, carbon dioxide tension, haemoglobin and lactate from both ABG and VBG analysis. By using following formula, we calculated arterial oxygen content (CaO_2), venous oxygen content (CvO_2), difference between venous and arterial oxygen content ($C(a\text{-}v)O_2$), oxygen extraction ratio (O_2ER), difference between arterial and venous carbon dioxide content $P(v\text{-}a)CO_2$, and $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio [22].

$CaO_2 = (1.34 \times SaO_2 \times Hb) + (0.003 \times PaO_2)$

$CvO_2 = (1.34 \times SvO_2 \times Hb) + (0.003 \times PcvO_2)$

$C(a–v)O_2 = CaO_2 – CcvO_2$

$P(v\text{-}a)CO_2$ gap $= PvCO_2 – PaCO_2$

$P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio $= P(v\text{-}a)CO_2$gap$/C(a–v)O_2$

$O_2ER = C(a\text{-}v)O_2/CaO_2$

Patients were followed during 72 hours of ICU stay, the ICU length of stay and ICU mortality were computed.

STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS version 20.0 software (SPSS Inc, USA). One-way ANOVA test and independent sample t-test were used to compare categorical and continuous variables respectively. Data were presented as mean±SD or proportion as appropriate. The p-value less than 0.05 was considered to be significant.

RESULTS

The demographic and the preoperative CPB data have been presented in [Table/Fig-1-3]. Age ranged between the one month to 84 months.

White Blood Cell (WBC) and Haemoglobin (Hb), creatinine and platelet count till third postoperative day are described in [Table/Fig-4]. There was significant fall in platelet count on second postoperative day, however, the count started recovering from day three.

Variables	Height (cm)	Weight (kg)	Body surface area (kg/m^2)	CPB time (min)	Cross clamp time (min)
Mean	71.3303	6.7418	0.3837	95.3545	63.3107
Median	69.0000	6.2000	0.3531	87.0000	57.0000
Standard deviation	16.11076	3.05324	0.14125	43.17037	34.01961
Range	43-120	2.3-14	0.17-0.74	95.3-43.1	63.3-34.0

[Table/Fig-1]: Demographic profile of the study population.

Preoperative CPB	Artery (Mean±SD)	Vein (Mean±SD)	p-value
pH	7.343±0.09	7.336±0.09	0.5647
PCO_2 (mm Hg)	43.65±10.30	45.11±9.90	0.2850
SpO_2 (%)	89.58±15.56	70.82±16.51	<0.001
Hb (gm/dl)	12.59±9.47	11.32±5.67	0.2288
PO_2 (mm Hg)	180.65±160.9	45.86±17.01	<0.001

[Table/Fig-2]: Describes data of pre CPB arterial and venous ph, PCO_2, PO_2, Hb, SpO_2 and temperature.
* CPB: Cardiopulmonary bypass, PCO_2:Partial pressure of carbon dioxide, SpO_2: Saturation of oxygen, Hb: Haemoglobin, PO_2: Partial pressure of oxygen.

DISCUSSION

Difference between mixed venous and arterial CO_2content reflect the cardiac output, as per Fick equation. A linear relationship between venous to arterial CO_2 content difference and cardiac output has been described [22].

Variables	10 minute after CPB (Mean±SD)	30 minute after CPB (Mean±SD)	Off CPB (Mean±SD)	p-value
pH Artery	7.38±0.07	7.43±0.07	7.35±0.09	<0.001
pH Vein	7.33±0.07	7.39±0.07	7.31±0.08	<0.001
PCO_2Artery (mmHg)	42.87±8.61	37.01±6.42	40.59±9.05	<0.001
PCO_2 Vein (mmHg)	50.08±9.08	44.65±7.68	47.41±10.52	<0.001
$P(v\text{-}a)CO_2$ (mmHg)	7.20±3.48	7.36±3.92	6.68±5.55	0.490
CaO_2(ml O_2/dl)	12.77±1.54	13.16±3.37	15.44±2.86	<0.001
CvO_2 (ml O_2/dl)	9.63±2.16	10.21±3.41	12±2.80	<0.001
$C(a\text{-}v)O_2$ (ml O_2/dl)	3.14 ± 1.36	3.08±1.40	4.54±4.20	<0.001
$P(v\text{-}a)CO_2$/ $C(a\text{-}v)CO_2$	2.73±1.55	2.90±1.68	2.00±3.23	0.009
SpO_2 Artery (%)	107.31±85.72	99.10±3.87	94.29±9.93	0.149
SpO_2 Vein (%)	78.29±12.74	79.55±15.05	74.19±12.58	0.009
Lactate Artery (mg/dl)	4.24±2.14	3.95±2.51	4.31±3.48	0.593
Lactate Vein (mg/dl)	4.12±1.86	3.76±2.27	4.28±3.03	0.270
Sugar artery (gm %)	195.98±85.10	234.06±79.06	249.46±88.58	<0.001
Sugar vein (gm %)	191.5±83.22	224.06±81.04	238.40±81.92	<0.001
Hb Artery (gm %)	9.02±1.08	9.80±1.20	12.67±9.74	<0.001
Hb Vein (gm %)	9.00±1.06	10.30±3.59	11.84±1.98	<0.001
PO_2 Artery (mmHg)	270.42±109.6	261.64±70.7	176.49±132.17	<0.001
PO_2 Vein (mmHg)	50.33±27.43	48.05±16.33	52.96±58.76	0.641
Do_2 (ml O_2/ min)	290.90±35.02	301.62±76.19	----------	0.181

[Table/Fig-3]: Shows data and calculation after 10, 30 minutes after CPB and off CPB initiation.
* PCO_2: Pressure of carbon dioxide, SpO_2: Saturation of oxygen, PO_2: Partial pressure of oxygen, DO_2: Oxygen delivery, Hb: Haemoglobin, CaO_2: Arterial oxygen concentration, CvO_2: Ventricle oxygen concentration (a-v) O_2: Difference of Arterial and venous oxygen content.

According to the modified Fick equation applied to CO_2, PCO_2 gap is linearly related to CO_2 production (VCO_2) and inversely related to cardiac index. Considering the respiratory quotient (VCO_2/VO_2 ratio), VCO_2 is directly related to O_2 consumption (VO_2) [20,23]. Under conditions of adapted cardiac output to VO_2, even if the CO_2 produced is higher than normal because of an additional anaerobic CO_2 production, in the presence of sufficient flow to wash out the CO_2 produced by the tissues, the $P(v\text{-}a)CO_2$ should not be increased. Conversely, low blood flow can result in a widening of the $P(v\text{-}a)CO_2$ even if no additional CO_2 production occurs because of a CO_2 stagnation phenomenon [19,24]. Venous hypercarbia is a marker of limited blood flow during cardiac arrest and shock states [5,9,25].

Mekontso-Dessap A et al., suggested that the $P(v\text{-}a)CO_2/(Ca\text{-}v)CO_2$ ratio might be a reflection of anaerobic metabolism, demonstrating a positive correlation between this parameter and lactate [9]. A study by Neviere R et al., thus demonstrated the key role of microvascular blood flow on gastric CO_2 accumulation [23].

Meanwhile, Creteur J et al., found a significant correlation among sublingual CO_2, gastric mucosal CO_2 and microcirculatory heterogeneity in human septic shock during dobutamine infusion and suggested that the primary determinant of tissue CO_2 accumulation was the microcirculatory blood flow [26]. Hence, there is an evident

	Preoperative (Mean±SD)	Postoperative Day 1 (Mean±SD)	Postoperative Day 2 (Mean±SD)	Postoperative Day 3 (Mean±SD)	p-value
Total count (/Cumm)	10802±3726.8	16240.4±6660.4	13386.3±5043.1	11968.4±5945.4	<0.001
Hb (gm %)	13.07±2.78	14.29±9.02	11.98±1.87	13.23±13.75	0.326
Creatinine (mg/dl)	0.452±0.09	0.505±0.15	0.570±0.32	0.527±0.26	0.001
Platelet (/Cumm)	3409.6±1288.8	1818.4±839.08	1336.9±758.6	1468.8±1044.3	<0.001

[Table/Fig-4]: Postoperative laboratory data.

link between blood flow and tissue or local CO_2 accumulation conducting to increase tissue or venous-to-arterial CO_2 differences, but sometimes normal macro haemodynamics does not prevent elevation of $P(v\text{-}a)CO_2$.

In a study by Mekontso-Dessap A et al., global anaerobic metabolism reflected as increase in $P(v\text{-}a)CO_2$ to oxygen consumption ratio [9].

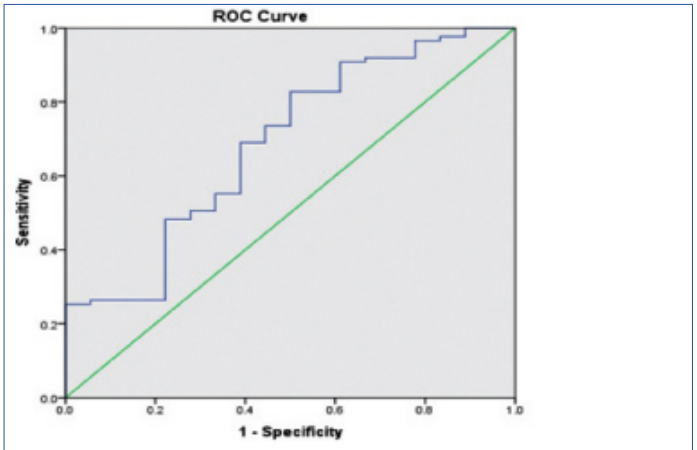
During conditions of tissue hypoxia but with preserved blood flow (even though during anaerobic metabolism carbon dioxide production (VCO_2) decreases less than oxygen consumption (VO_2)), venous blood flow might be high enough to ensure adequate washout of the CO_2 produced by hypoxic cells, thereby preventing a $P(v\text{-}a)CO_2$ increase.

The increase in venous PCO_2 would reflect a state of insufficient flow relative to CO_2 production [26]. This condition has been demonstrated previously. Indeed, Vallet B et al., showed that the venous-to-arterial CO_2 gap (PCO_2 gap) increased during low blood flow-induced tissue hypoxia (ischemic hypoxia) while it remained unchanged during hypoxemia-induced hypoxia (hypoxic hypoxia) [18].

Our study, unlike others, was performed in paediatric cardiac surgical patients, who underwent CPB during cardiac surgery.

We hypothesize that $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$, could be a better marker of anaerobic metabolism and low flow during CPB. Most of the studies performed, were in adult group of patients having sepsis. Our study has proved that $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ can detect anaerobic metabolism earlier than lactate.

ROC curve at 30 minute of cardiopulmonary bypass time shows that $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ was more specific and sensitive than lactate to detect anaerobic metabolism. We suggest to use $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ as a marker to detect low flow on CPB [Table/Fig-5]. In our study, we found that platelet count decrease was significant on second postoperative day. However, recovery started from third postoperative day.



Area Under the Curve

Test Result Variable(s): CPB_30_MIN_AFTER_ratio

Area	Std. Error	Asymptotic Sig.[a]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.686	0.071	0.013	0.548	0.825

a. Null hypothesis: true area = 0.5

[Table/Fig-5]: ROC curve of patients whose lactate level were high, compared with $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio.

LIMITATION

Studies involving large population and multiple centers are required to support the study, as our present study is single centric and with a small size.

CONCLUSION

We suggest to use $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio as a marker to detect anaerobic metabolism on CPB. Unfortunately, the calculation of CO_2 content is very complex and subject to errors due to the number of variables included in the formula.

REFERENCES

[1] Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Medicine. 2008;34(1):17-60.
[2] Shoemaker WC, Appel PL, Kram HB. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. Crit Care Med. 1988;16:1117–20.
[3] Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Eng J Med. 2001;345:1368–77.
[4] Russell JA, Phang PT. The oxygen delivery/consumption controversy. Approaches to management of the critically ill. Am J RespirCrit Care Med. 1994;149:533–37.
[5] Mecher CE, Rackow EC, Astiz ME, Weil MH. Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. Crit Care Med. 1990;18:585–89.
[6] Adrogue HJ, Rashad MN, Gorin AB, Yacoub J, Madias NE. Assessing acid–base status in circulatory failure. Differences between arterial and central venous blood. N Engl J Med. 1989;320:1312–16.
[7] Ospina-Tascón GA, Umaña M, Bermúdez WF, Bautista-Rincón DF, Valencia JD, Madriñán HJ, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Medicine. 2016;42(2):211-21.
[8] Vallee F, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? Intensive Care Med. 2008;34:2218–25.
[9] Mekontso-Dessap A, Castelain V, Anguel N, Bahloul M, Schauvliege F, Richard C, et al. Combination of venoarterial PCO_2 difference with arteriovenous O_2 content difference to detect anaerobic metabolism in patients. Intensive Care Med. 2002;28:272–77.
[10] Van Beest PA, Lont MC, Holman ND, Loef B, Kuiper MA, Boerma EC. Central venous–arterial pCO_2 difference as a tool in resuscitation of septic patients. Intensive Care Med. 2013;39:1034–39.
[11] Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM. Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. Chest. 1989;95:1216-21.
[12] Donati A, Loggi S, Preiser JC, Orsetti G, Munch C, Gabbanelli V, et al. Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. Chest. 2007;132:1817-24.
[13] Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Changes in central venous saturation after major surgery, and association with outcome. Crit Care. 2005;9:R694-99.
[14] Futier E, Constantin JM, Petit A, Chanques G, Kwiatkowski F, Flamein R, et al. Conservative versus restrictive individualized goal-directed fluid administration in major abdominal surgery: a prospective randomized trial. Arch Surg. 2010;145(12):1193-200.
[15] Pearse RM, Hinds CJ. Should we use central venous saturation to guide

management in high-risk surgical patients? Crit Care. 2006;10:181.
[16] Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI. Multicenter study of central venous oxygen saturation ($ScvO_2$) as a predictor of mortality in patients with sepsis. Ann Emerg Med. 2010;55:40.e1-46.e1.
[17] Cuschieri J, Rivers EP, Donnino MW, Katilius M, Jacobsen G, Nguyen HB, et al. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. Intensive Care Med. 2005;31:818-22.
[18] Vallet B, Teboul JL, Cain S, Curtis S Venoarterial CO_2 difference during regional ischemic or hypoxic hypoxia. J Appl Physiol. 2000;89:1317-21.
[19] Lamia B, Monnet X, Teboul JL. Meaning of arterio-venous PCO_2 difference in circulatory shock. Minerva Anestesiol. 2006;72:597-604.
[20] Bakker J, Vincent JL, Gris P, Leon M, Coffernils M, Kahn RJ. Veno-arterial carbon dioxide gradient in human septic shock. Chest. 1992;101:509-15.
[21] Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock. 2009;32(1):35-39.
[22] Mesquida J, Saludes P, Gruartmoner G, Espinal C, Torrents E, Baigorri F, et al. Central venous-to-arterial carbon dioxide difference combined with arterial-to-venous oxygen content difference is associated with lactate evolution in the haemodynamic resuscitation process in early septic shock. Critical Care. 2015;19:126.
[23] Neviere R, Chagnon JL, Teboul JL, Vallet B, Wattel F. Small intestine intramucosal pCO_2 and microvascular blood flow during hypoxic and ischemic hypoxia. Crit Care Med. 2002;30:379-84.
[24] Neviere R, Mathieu D, Chagnon JL, Lebleu N, Wattel F. The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. Am J Respir Crit Care Med. 1996;154:1684–88.
[25] Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI. Difference in acid–base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med. 1986;315:153–56.
[26] Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL. Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med. 2006;32:516–23.

PARTICULARS OF CONTRIBUTORS:
1. Professor and Head, Department of Cardiac Anaesthesia, U. N. Mehta Institute of Cardiology and Research Center, Ahmedabad, Gujarat, India.
2. Chief Perfusionist, Department of Perfusion, U. N. Mehta Institute of Cardiology and Research Center, Ahmedabad, Gujarat, India.
3. Resident, Department of Cardiac Anaesthesia, U. N. Mehta Institute of Cardiology and Research Center, Ahmedabad, Gujarat, India.
4. Perfusionist, Department of Perfusion, U. N. Mehta Institute of Cardiology and Research Center, Ahmedabad, Gujarat, India.
5. Research Associate, Department of Research, U. N. Mehta Institute of Cardiology and Research Center, Ahmedabad, Gujarat, India.
6. Postgraduate Student, Department of Perfusion, U. N. Mehta Institute of Cardiology and Research Center, Ahmedabad, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Ramesh Patel,
Professor and Head, Department of Cardiac Anaesthesia, U. N. Mehta Institute of Cardiology and Research Center,
Civil Hospital Campus, Asarwa, Ahmedabad-380016, Gujarat, India.
E-mail: dr.ramesh33@gmail.com

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