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A STUDY OF LACTIC ACID PRODUCTION AND RECOVERY RATE IN THE COPD AND NORMAL PERSON AFTER AN EXERCISE

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ABBREVIATION

COPD	**Chronic Obstructive Pulmonary Diseases**
• OBLA	Onset Of Blood Lactate Accumulation
• FEV1	Forced Expiratory Volume In 1 Second
• FVC	Forced Vital Capacity
• PEFR	Peak Expiratory Flow Rate
• CB	Chronic Bronchitis
• CAL	Chronic Airflow Limitation
• COLD	Chronic Obstructive Lung Disease
• CO_2	Carbon dioxide
• P CO_2	Partial Pressure Of Carbon Dioxide
• O_2	Oxygen
• GOLD	Global Initiative for Chronic Obstructive Lung Disease
• SaO_2	Saturation Of Oxygen
• SBP	Systolic Blood Pressure
• DBP	Diastolic Blood Pressure
• HR	Heart Rate
• HRR	Heart Rate At Rest
• HR1	Heart Rate Immediately After Exercise
• RR	Respiratory Rate
• RRR	Respiratory Rate At Rest
• BLA	Blood Lactate
• BLAR	Blood Lactate At Rest
• BLA1	Blood Lactate Immediately After Exercise
• BLA2	Blood Lactate After 15 Minutes Of Exercise
• BLA3	Blood Lactate After 30 Minutes Of Exercise
• SaO_21	Saturation Of Oxygen Immediately After Exercise
• I.H.D.	Ischemic Heart Disease
• L^+	Lactate Plus
• Gm	Grams
• L	Liter
• CS	Citrate synthase
• HADH	3-hydroxyacyl CoA dehydrogenase

- NADH — Nicotinamide Adenine Dinucleotide
- LDH — Lactate Dehydrogenase
- ATP — Adenosine triphosphate
- PFT — Pulmonary Function Test
- P_H
- CF — Cystic Fibrosis
- AECOPD — Acute Exacerbation of COPD
- BMRC — British Medical Research Council
- ATS — American Thoracic Society
- LVRS — Lung Volume Reduction Surgery
- TCA — Tricarboxylic Acid Cycle
- VA/Q — Ventilation/Perfusion
- PFK — Phosphofructokinase
- PHT — Pulmonary Hypertension
- PDH — Pyruvate Dehydrogenase
- LT — Lactate Threshold
- Mm — milimole
- TUT — Time Under Tension
- 6MWT — Six Minute Walk Test
- PRE — Perceived Rate Of Exertion

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has only recently been seen as a multi-systemic rather than a respiratory system disease [(1)] It is acknowledged that the inflammation which occurs and installs in COPD leads to remodeling of the airway, with consequent impaired pulmonary mechanism and obstructed air flow [(2)]

Chronic obstructive pulmonary disease (COPD) has been variously labeled in the past as chronic bronchitis (CB) and emphysema, chronic nonspecific respiratory disease, chronic airway obstruction (CAO), chronic airflow limitation (CAL) and chronic obstruction lung disease (COLD) depending upon the understanding of the path physiology and clinical features of the syndrome of chronic cough and/or airways obstruction. It is only in the last century that the disease has been better understood. Yet, the confusion in the terminology has persisted till now. COPD is presently accepted as an overall umbrella term for a variety of clinical disorders with chronic bronchitis at the one and emphysema at the other end of the spectrum.

Globally, COPD has emerged as the major cause of morbidity and mortality expected to become the 3rd most leading cause of death and the 5th leading cause of loss of 'Disability Adjusted Life Years' (DALYs) as per projection of the Global Burden of Disease Study (GBDS).The region-wise projections for the developing countries including India were even worse. [(3)]

Extra pulmonary manifestations in COPD, in addition to pulmonary component, are common. It has been observed in the ECLIPSE study that co morbidities were significantly higher in patients with COPD than in smokers and never smokers [(4).] The important co morbidities associated with COPD are cardiovascular disorders (coronary artery disease and chronic heart failure, hypertension), metabolic diseases (diabetes mellitus, metabolic syndrome and obesity), bone disease (osteoporosis and osteopenia), stroke, lung cancer, cachexia, skeletal muscle weakness, anemia, depression and cognitive decline [(5)] [(6)].

Worldwide, COPD affects 329 million people or nearly 5% of the population. In 2011, it ranked as the fourth leading cause of death, killing over 3 million people. [(7)].The number of deaths is projected to increase due to higher smoking rates and an aging population in many countries. [(8)] It resulted in an estimated economic cost of $2.1 trillion in 2010. [(9)]

It is generally known that a substantial portion of patients with chronic obstructive pulmonary disease (COPD) develop lactic acidosis early in exercise and at very low work rates [(10)] [(11)] Lactic acidosis is unfavorable, since it puts additional stress on these patients'

limited ventilatory system during exercise. Recently, evidence has become available that a reduced oxidative capacity of skeletal muscle correlates with the accelerated lactate (La) response to exercise in COPD [12]

It has been described that COPD patients develop early lactic acidosis during lower limb exercises, which enhances the ventilator output and imposes certain limits to the exercise tolerance. [13]

EXERCISE AND LACTATE

The effect of lactate production on acidosis has been the topic in the field of exercise physiology. The production of lactate does result in a hydrogen ion, potentially resulting in a fall in pH. However, the hydrogen ion is quickly buffered by bicarbonate which forms an intermediary in the blood stream which is quickly converted into water and carbon dioxide. CO_2 is transported to the lungs and exhaled to maintain acid-base status. This is the reason for the increased respiratory rate with the accumulation of lactate in the blood. This process can be written as chemical equation:

Lactic Acid →dissociates→ Lactate + H^+

$H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$ (CO_2 is expired at the lungs to maintain pH)

The bicarbonate buffering system is extremely efficient at removing the acidifying hydrogen ion and expelling it form the body in the form of carbon dioxide. The only remaining by product of anaerobic metabolism is lactate.

Increasing partial pressure of CO_2, PCO_2, also causes an increase in $[H^+]$. During exercise, the intramuscular lactate concentration and PCO_2 increase, causing an increase in $[H^+]$, and thus a decrease in pH. Strenuous anaerobic exercise causes a lowering of pH and pain, called acidosis.

The by-product of anaerobic glycolysis, lactate, has traditionally been thought to be detrimental to muscle function. However, this appears likely only when lactate levels are very high. Elevated lactate levels are only one of many changes that occur within and around muscle cells during intense exercise that can lead to fatigue. Fatigue, that is muscular failure, is a complex subject. Elevated muscle and blood lactate concentrations are a natural consequence of any physical exertion. The effectiveness of anaerobic activity can be improved through training. [14] [15]

- At slightly higher exercise intensity than lactate threshold a second increase in lactate accumulation can be seen and is often referred to as the onset of blood lactate accumulation or OBLA. OBLA generally occurs when the concentration of blood lactate reaches about 4mmol/L [16]

Owing to its major and better recognized burden from both individual and societal perspectives, chronic obstructive pulmonary disease (COPD) is an area of intensive epidemiological, fundamental and clinical research, leading to the publication of more than 10,000 papers each year in the Pub Med database. Among these, many report important advances in the understanding of and care for COPD. Epidemiological aspects are the topic of another manuscript in this issue of the European Respiratory Review. [17]

Patients with COPD have generally limited exercise capacity because of the reduced ventilatory capacity. During a progressive exercise test, generally a patient with COPD will reach his maximum work rate earlier and be unable to continue exercise.

Most often, treatment of the dyspnoea of patients with COPD is designed to improve pulmonary mechanics by the use of medicine and control or reduce the chances of infection. However, reduction of the metabolic acidosis during the exercise by exercise training is also an important approach to reduce the ventilatory drive and ultimately exertional dyspnoea and improve the exercise capacity of a patient. [11]

In patients with COPD strength and endurance exercise capacity are impaired. [18] [19] Exercise capacity may be affected by many factors such as ventilator limitation, dynamic hyperinflation and diminished oxygen uptake in the lung. [20] In addition, impaired exercise capacity could be caused by factors outside the lung, such as early lactate production, [10] [21] [22] muscle dysfunction1 and cardiovascular deconditioning (e.g. higher heart rate and lower stroke volume during exercise) [23] [24] which may at least be partially induced by sedentary lifestyle due to dyspnea. [25]

In so many study it is shown that early lactate is the one of the factor for the exercise limitation in the COPD patients but how early it starts accumulating in the COPD patients compared to normal individual and how fast it is eliminated by CO_2 production is also important as this will determine the duration of exercise so this study is mainly to compare the rate of production and recovery of lactate in the COPD and in normal individual after an exercise.

OVERVIEW AND DEFINITIONS

The term chronic obstructive pulmonary disease, abbreviated COPD, or sometimes COLD (chronic obstructive lung disease), refers to a disease state characterized by the presence of airflow obstruction resulting from chronic bronchitis or emphysema. As defined in the recent American Thoracic Society guidelines statement regarding COPD" *COLD (chronic obstructive lung disease) is a treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and*

associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequence."

Similarly, the recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines as "a disease state characterized by airflow limitation that is not fully reversible, is abnormal inflammatory response of the lungs to noxious particles or gases" [26]

ETIOLOGY

Tobacco smoking is the most common cause of COPD, with a number of other factors such as air pollution and genetics playing a smaller role. [27] In our country, *bidi* smoking is an important factor in addition to cigarette smoking that causes COPD [28] .

It also appears that outdoor air pollutants are significant environmental triggers for AECOPD and chronic exposure to the traffic exposure affects the respiratory health conditions, from increasing symptoms to emergency department visits, hospital admissions and even mortality. Improving ambient air pollution and decreasing indoor biomass combustion exposure by improving home ventilation appear to be effective interventions that could substantially benefit the health of the general public. [29] [30]

PREVALENCE OF COPD GLOBALLU AND IN INDIA

The prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced. [31]

Globally, as of 2010, COPD affected approximately 329 million people (4.8% of the population) and is slightly more common in men than women [32] this is as compared to 64 million being affected in 2004. [33]

By 2020, COPD is predicted to be the third leading cause of death and fifth leading cause of chronic disability worldwide. [34]

The current prevalence of COPD in India is unclear because of variation in study design and lack of adherence to strict protocol of the definition of COPD. [35]

SYMPTOMS

The characteristic symptoms of COPD are chronic and progressive dyspnoea, cough and sputum production that can be variable from day to day [36]. Chronic cough and sputum production may precede the development of airflow limitation by many years. Conversely significant airflow limitation may develop without chronic cough and sputum production.

CLASSIFICATION OF SEVERITY OF COPD

The global initiative for chronic obstructive lung disease (GOLD) has proposed a universal guideline for the classification of COPD on the basis of both spirometry and clinical symptoms to define stage of the disease. [37]

Universal Guideline for the Classification of Disease

	PREDICTED FEV1/FVC	FEV1
MILD COPD	<70%	>80%
MODERATE COPD	<70%	<50% to 80%
SEVERE COPD	<70%	<30%

PATHOPHYSIOLOGY OF COPD

COPD comprises pathological changes in four different compartments of the lungs (central airways, peripheral airways, lung parenchyma and pulmonary vasculature), which are variably present in individuals with the disease [31]

The path physiology of chronic obstructive pulmonary disease (COPD) is complex and can be attributed to multiple components: mucociliary dysfunction, airway inflammation and structural changes, all contributing to the development of airflow limitation, as well as an important systemic component. [38]

PULMONARY HYPERTENSION:

P.H.T may develop late in the course of COPD and is due mainly to hypoxic vaso constriction of small pulmonary arteries eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually right side cardiac failure.

EXACERBATIONS:

An exacerbation of respiratory symptoms often occurs in patients with COPD triggered by infection with bacteria or viruses, environmental pollutants or unknown factors. During this period there is more hyperinflation which leads to increased dyspnoea at the end.

SYSTEMIC FEATURES:

It is increasingly recognized that many patients with COPD have comorbities that have a major impact on quality of life and survival. Airflow limitation and particularly hyperinflation affect cardiac function and gas exchange. Inflammatory mediators in the circulation may contribute to skeletal muscle wasting and cachexia and may initiate or worsen comorbities such as I.H.D., Heart failure, osteoporosis, normocytic anemia, diabetes, metabolic syndrome and depression.

Study show that the earliest manifestation of chronic obstructive pulmonary disease (COPD) is an increase in residual volume suggesting that the natural history of COPD is a progressive increase in gas trapping with a decreasing vital capacity (VC). The reduction in VC forces the forced expiratory volume in 1 s to decline with it. This is aggravated by rapid shallow breathing leading to dynamic hyperinflation. [39] [40] [41] [42]

MANAGEMENT OF COPD

An effective COPD management plan includes four components: (1) assess and monitor disease; (2) reduce risk factors; (3) manage stable COPD; (4) manage exacerbations. The goals of effective COPD management are to: [43]

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Reduce mortality

Appropriate diagnosis and management (from a pharmacologic and nonpharmacologic perspective) of COPD and its associated comorbidities are important to ensure optimal patient care. An evolving understanding of COPD as a multimorbid disease that affects an aging population, rather than just a lung-specific disease, necessitates an integrated, tailored disease-management approach to improve prognoses and reduce costs. [44]

PHARMACOLOGICAL THERAPY IN STABLE COPD:

Pharmacological therapy or drug which is used in the management of COPD is to reduce the different symptoms which is associated with the COPD. The following group of the drug is used

1. BRONCHODILATOR:

This medication is given as and when it is needed. It improves the FEV1 or other spirometry values by altering the tone of the smooth muscle. This drug widens the airways so it easy the expiration and so it improves the hyperinflation of the lung during the exercise and rest

2. ANTICHOLINERGICS :

The most important action of the anticholinergic drug on COPD is it block the effects of acetylcholine on muscarinic receptors and modify the transmission at the pre-ganglionic junction

3. METHYLXANTHINE:

Controversy remains about the exact effects of this drug as it has been reported to have a range of non-bronchodilator action. Change in the inspiratory muscle function has been reported by theophyline.

4. CORTICOSTEROIDS: It improves the symptoms, lung function and quality of life and reduces the frequency of exacerbations in patients of COPD.

5. ORAL CORTICOSTEROIDS:

The details of corticosteroids are given below in table.

NON-PHARMACOLOGICAL THERAPY IN COPD

- **SMOKING CESSATION**
- **PULMONARY REHABILITATION:**

American Thoracic Society defined pulmonary rehabilitation as "a multidisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy"

Pulmonary rehabilitation comprises a variety of interventions grouped into three main categories: Exercise training, education, and psychological support. Typically, patients participate in a programme of exercise rehabilitation 2–3 times a week for 6–12 weeks, at the same time being encouraged to incorporate breathing and stretching exercises as part of their daily routine. The physiological rationale for pulmonary rehabilitation in COPD is primarily based on its effect on peripheral muscle dysfunction. A recent meta-analysis demonstrated that pulmonary rehabilitation is effective in reducing dyspnoea and fatigue as well as improving patients' sense of control (mastery) over their condition. Without compliance with a maintenance programme these improvements will diminish with time. The value of various components of rehabilitation, programme length, the required degree of supervision, the intensity of training and the best approach to maintaining programme adherence represent issues that remain to be explored. [45] [46] [47] [48] [49] [50]

- **RELAXATION**

Premature expiratory flow limitation is naturally countered by pursed lip breathing in some people, while hyperventilation may also be a component of exacerbation or episodes of breathlessness for these reasons it has been popular to include relaxation exercises or breathing retraining in rehabilitation classes. [45]

- **NON INVASIVE VENTILATION**
- **LONG TERM OXYGEN THERAPY**

- **LUNG VOLUME REDUCTION SURGERY**
- **NUTRIOTIONAL SUPPLEMENTS**
- **VACCINATION**

Several viruses and bacteria play a role in the exacerbation in the COPD which leads to morbidity so it is recommended that health care professionals should use the vaccination for the COPD patients against influenza, pneumococcal, pertusis. [51] [52].

The managements of COPD are not only done by chest physician but it includes many other health care professionals like medical practitioners, nursing staff, respiratory therapist and patient as well. [53]

LACTATE: NORMAL VALUE AND UNIT

The units of measurement of lactate vary between laboratories. Some use milligrams per deciliter ($mg.dl^{-1}$), whereas others use milimoles per liter ($mmol.l^{-1}$) conversion between these units is based on knowing that the molecular weight of lactic acid is 90, hence

$mg.dl/L = mmol.l^{-1}*9$

or

$Mmol/L = mg.dl^{-1}*0.111$

The normal reference value for blood lactate at rest is 5-20 $mg.dl^{-1}$

Or 0.5 to 2.2 mmol/L [54]

LACTATE PRODUCTION

Before we understand that how lactate is produced it is necessary to understand the normal metabolic pathway of the energy system in human body which is very well shown here in diagram.

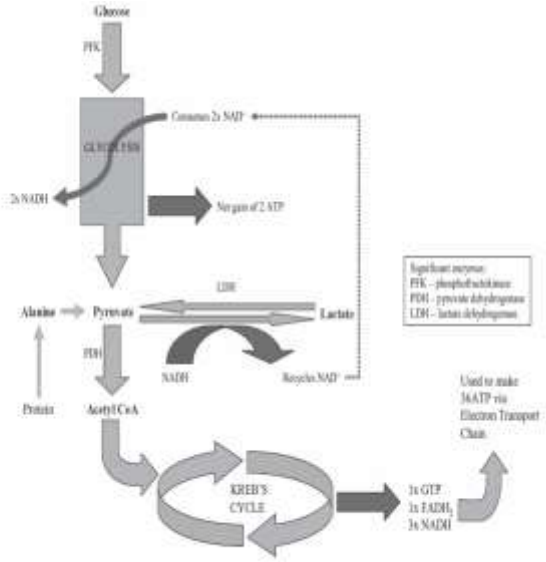
The citric acid cycle — also known as the tricarboxylic acid cycle (TCA cycle), or the Krebs cycle,is a series of chemical reactions used by all aerobic organisms to generate energy through the oxidation of acetate derived from carbohydrates, fats and proteins into carbon dioxide and chemical energy in the form of adenosine triphosphate (ATP). In addition, the cycle provides precursors of certain amino acids as well as the reducing agent NADH that is used in numerous other biochemical reactions. Its central importance to many biochemical pathways suggests that it was one of the earliest established components of cellular metabolism and may have originated abiogenically.

The name of this metabolic pathway is derived from citric acid (a type of Tricarboxylic acid) that is consumed and then regenerated by this sequence of reactions to complete the cycle. In addition, the cycle consumes acetate (in the form of acetyl-CoA) and

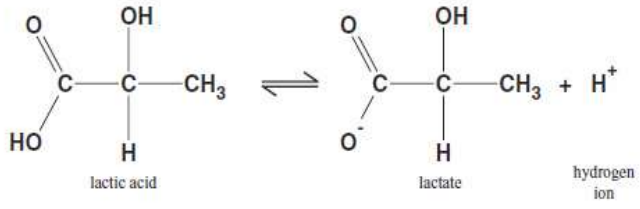
water, reduces NAD+ to NADH, and produces carbon dioxide as a waste byproduct. The NADH generated by the TCA cycle is fed into the oxidative phosphorylation (electron transport) pathway. The net result of these two closely linked pathways is the oxidation of nutrients to produce usable chemical energy in the form of ATP.

Lactate production occurs whenever the rate of pyruvate production from glycolysis exceeds glucose oxidation by the mitochondria. Therefore, for increased lactate production to be important physiologically, mitochondrial glucose oxidation must decrease under conditions known to result in increased gluconeogenesis.

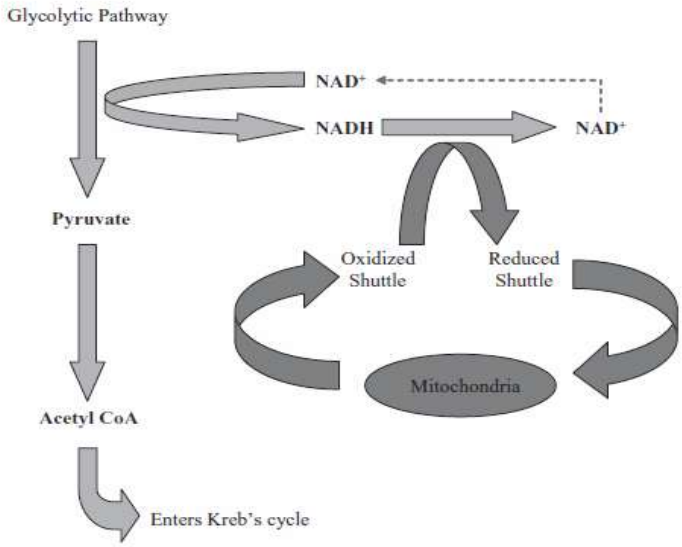
Above all this process is shown in the figure below. [55]



Glycolysis,Kreb's cycle and oxidative phosphorylation



The dissociation of lactic acid



The Ox-Phos Shuttle

During rest and moderate exercise, some lactate continually forms in two ways.1-energy metabolism of red blood cells that contain no mitochondria and 2-limitations posed by enzyme activity in muscle fibers with high glycolytic capacity. Any lactate that forms in this manner readily oxidized for energy in neighboring muscle fibers with high oxidative capacity or in more distant tissue such as the heart and ventilatory muscles. Consequently lactate does not accumulate because its removal rate equals its rate of production. (16)

During intense exercise, the respiratory chain cannot keep up with the amount of hydrogen atoms that join to form NADH. NAD^+ is required to oxidize 3-phosphoglyceraldehyde in order to maintain the production of anaerobic energy during glycolysis. During anaerobic glycolysis, NAD^+ is "freed up" when NADH combines with pyruvate to form lactate (as mentioned above). If this did not occur, glycolysis would come to a stop. However, lactate is continually formed even at rest and during moderate exercise. This occurs due to metabolism in red blood cells that lack mitochondria, and limitations resulting from the enzyme activity that occurs in muscle fibers having a high glycolytic capacity.

During power exercises such as sprinting, running, cycling when the rate of demand for energy is high, glucose is broken down and oxidized to pyruvate, and lactate is produced from the pyruvate faster than the tissues can remove it, so lactate concentration begins to rise. Once the production of lactate is occurs it regenerates NAD^+, which is used up in the creation of pyruvate from glucose, and this ensures that energy production is maintained and exercise can continue. The increased lactate produced can be removed in two ways:

- Oxidation back to pyruvate by well-oxygenated muscle cells

• Pyruvate is then directly used to fuel the Krebs cycle.

• Conversion to glucose via gluconeogenesis in the liver and release back into circulation; Cori cycle. [16]

• If not released, the glucose can be used to build up the liver's glycogen stores if they are empty.

ONSET OF BLOOD LACTATE ACCUMULATION:

During low-intensity, steady-rate exercise, blood lactate concentration does not increase beyond normal biologic variation observed at rest. As exercise intensity increases, blood lactate level exceed normal variation. Exercise intensity associated with a fixed blood lactate concentration that exceeds normal resting variation denotes the LT. This often coincides with a 2.5 milimoles (mM) value. A 4.0 mM lactate value indicates the onset of blood lactate accumulation (OBLA). [16]

An increased blood lactate concentration is common during physiological (exercise) and patho physiological stress (stress hyperlactataemia). In disease states, there is overwhelming evidence that stress hyperlactataemia is a strong independent predictor of mortality. However, the source, biochemistry, and physiology of exercise -induced and disease-associated stress hyperlactataemia are controversial. The dominant paradigm suggests that an increased lactate concentration is secondary to anaerobic glycolysis induced by tissue hypo perfusion, hypoxia, or both. [56] The normal plasma lactate concentration is 0.3–1.3 mmol litre_1. Considered once as a special investigation, it is increasingly measured automatically with the blood gas analysis. Plasma concentrations represent a balance between lactate production and lactate metabolism. In humans, lactate exists in the levorotatory isoform. Normal lactate production Glycolysis in the cytoplasm produces the intermediate metabolite pyruvate (Fig. 1). Under aerobic conditions, pyruvate is converted to acetyl CoA to enter the Kreb's cycle. Under anaerobic conditions, pyruvate is converted by lactate dehydrogenase (LDH) to lactic acid. In aqueous solutions, lactic acid dissociates almost completely to lactate and Hþ (pKa at 7.4 ¼ 3.9) (Fig. 2). Consequently, the terms lactic acid and lactate are used somewhat interchangeably. Lactate is buffered in plasma by NaHCO3. Tissue sources of lactate production include erythrocytes, perivenous hepatocytes, skeletal myocytes and skin. Basal lactate production is 0.8 mmol kg_1 h_1 (1300 mmol day_1). [55]

AIMS AND OBJECTIVES:

1. Aims of this study are to find out lactic acid production and recovery rate in the COPD patients and in normal individual.
2. Suggest suitable modifications in exercise/stress regimes to these patients.

EXCLUSION AND INCLUSION CRITERIA:

1. **Inclusion criteria :**

- Subjects willing to participate in the study
- Age between 40-80
- Patients with C.O.P.D

2. **Exclusion criteria :**

- Subjects who have acute attack of dyspnoea or any respiratory infection within last 3-4 weeks
- Subjects who does regular exercise.
- SpO2 is lower than 85%.

METHODS:

The present study was carried out in Shri Guru Gobindsinghji Hospital, Jamnagar with the basic aim of finding any difference between the rate of production and recovery in the COPD and in normal individual.

17 Stable patient who met the clinical diagnosis from the department of chest and respiratory diseases GGH, Jamnagar were recruited from GGH and the 17 normal individual matched with age were recruited from the physiotherapy department and other department for the measurement of lactate test.

Full approval was obtained from the MP SHAH MEDICAL COLLEGE RESEARCH ETHICAL COMMITTEE and all participants provided informed written consent.

OUTCOME MEASURE:

The primary outcome for this study is to measure sub maximal exercise lactate measurement and its recovery rate in patients of COPD as well as in age matched group of normal individuals. They were recruited in consecutive disorder: They had to be considered clinically stable without a history of any kind of infection or exacerbation and without changes in their medication during the last 3-4 week before the commencement of the test. We have excluded the patients whose resting SpO2 is lower than 85%.

All participants attached to the hospital, an initial baseline data were recorded. They were introduced with the physiotherapist, disease process, pulmonary function test machine, methods & methodology, equipment within ½ an hour. All participants were properly instructed about PFT machine. They were instructed to sit comfortably on the chair, and mouth piece was given to them and nose clip was kept on nose so subject may not inspire or expired through nose. After that they were instructed to do forceful expiration followed by forceful inspiration without any pause in between this cycle. Five to ten minutes rest was given after the PFT test is performed

After that subjects were asked to performed incremental exercise test on an electronic cycle ergometer. First 1 minute was only warm up with the cycling .After 1 minute of cycling workload was increased by applying more resistance at wheel (by tightening the knob of resistance) at every 60 seconds till the end of 5 minute. At every minute exertion level was asked by the chart of PRE (perceived rate of exertion) which is given here, at the end of test again the level of exertion was asked to each individual and the score was measured for each patient and the entire normal individual in the control group. Most of the patients and normal individuals PRE were between 13-17.

Rating of Perceived Exertion (RPE)	
6	No exertion at all
7	
	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Vey hard
18	
19	Extremely hard
20	Maximal exertion

Lactate level was measured with the instrument known as lactometer, before the exercise, immediately after the test, after 15 and 30 minutes of test.

The methods of using lactometer (Lactate Plus):

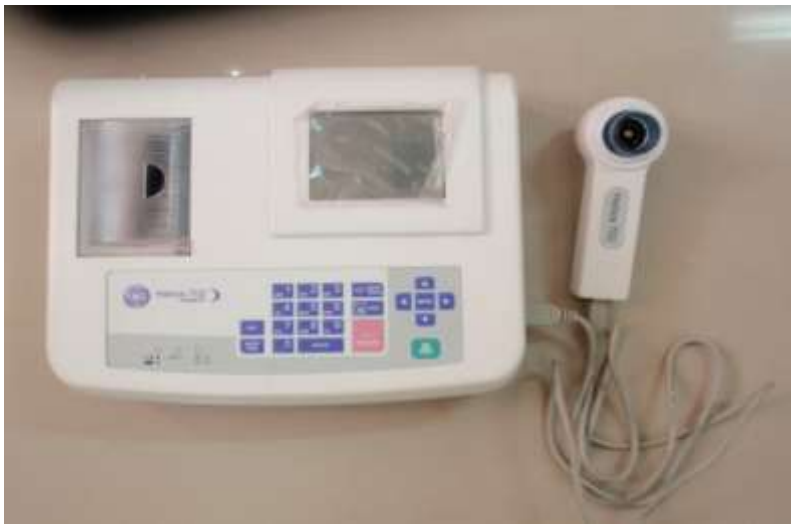
Lactate Plus (L^+, Nova Biomedical, and USA) uses an electrochemical lactate oxidase biosensor for the measurement of lactate in whole blood. The reliability and accuracy of lactate plus is checked with the laboratory –based analyzer, it was good compared to the lactate pro instrument. [57] [58] .A blood sample of 0.7 µL is required: sample analysis time is 11 seconds .Test strips used with the L^+ does not required calibration codes or specific calibration strips. The L^+ displayed good reliability and accuracy when compared to a laboratory based analyzer. [59]

For measurement of lactate one side index finger was chosen and pulp of distal phalanx was cleaned properly with spirit and cotton. After that lancet was used to prick the finger and blood is taken on strip after that strip was kept in lactometer instrument area for atleast 10-11 seconds till the value of lactate is shown on the display. Same way immediately after exercise, after 15 and 30 minutes procedure was done on alternative finger.

Materials to be used:

- Weighing scale
- Instrument to measure lactate i.e. lactometer
- Measure tape

- Sphygmomanometer
- PRE scale (Perceived rate of exertion)
- Watch
- Oxymeter
- Cycle
- PFT Machine
- Pen
- Paper



PFT instrument

- Lactometer
- Lancet and its instrument
- Measure tape
- Blood lactate measurement strip
- Oxymeter
- Pen

CHART NO 1 AGE

	COPD	CONTROL
AGE	56	59.94

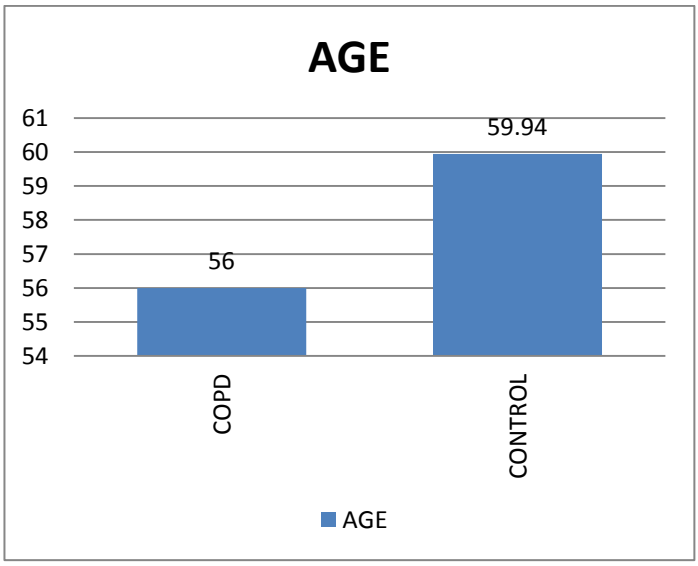
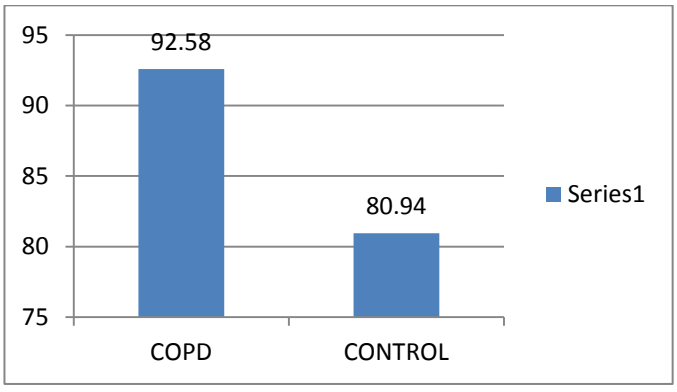


CHART NO 2-3 HRR AND SBP

	COPD	CONTROL
HRR	92.58	80.94



Systolic blood pressure

	COPD	CONTROL
SBP	130	127.41

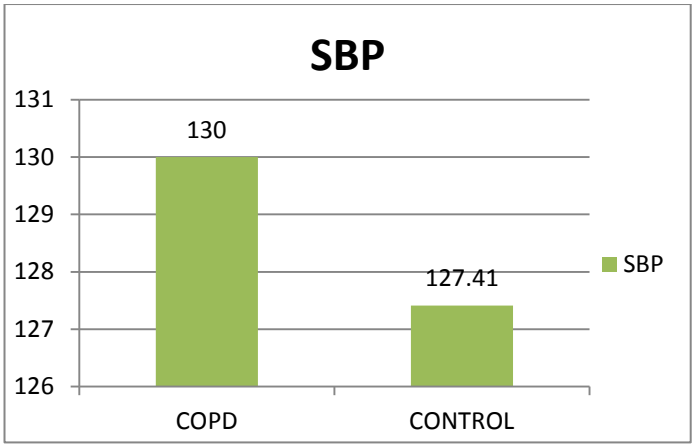
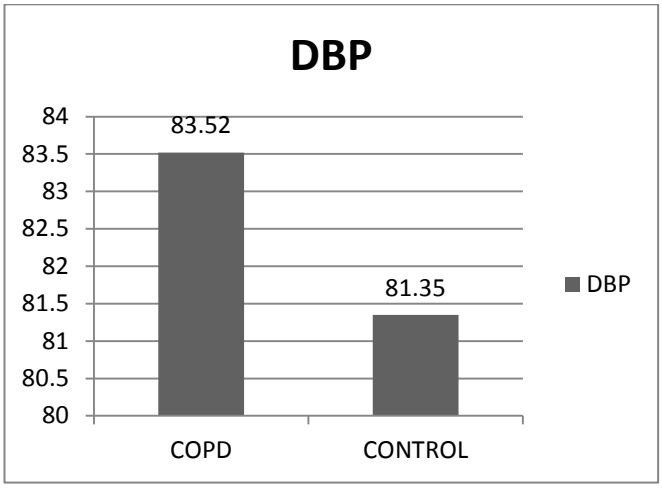


CHART NO 4-5 DBP AND SPO2

	COPD	CONTROL
DBP	83.52	81.35



	COPD	CONTROL
SPO2	96.35	97.29

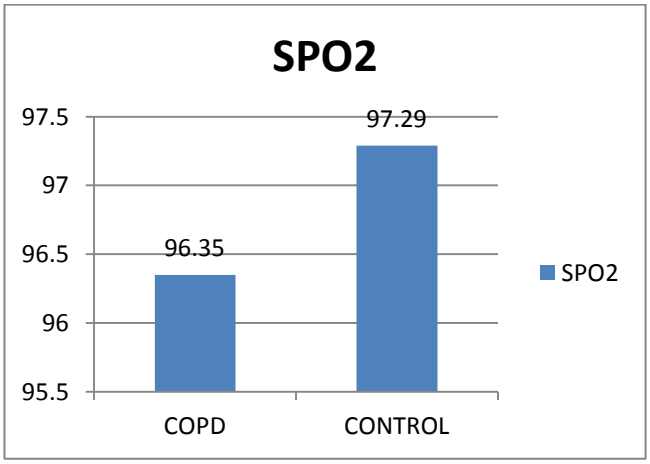
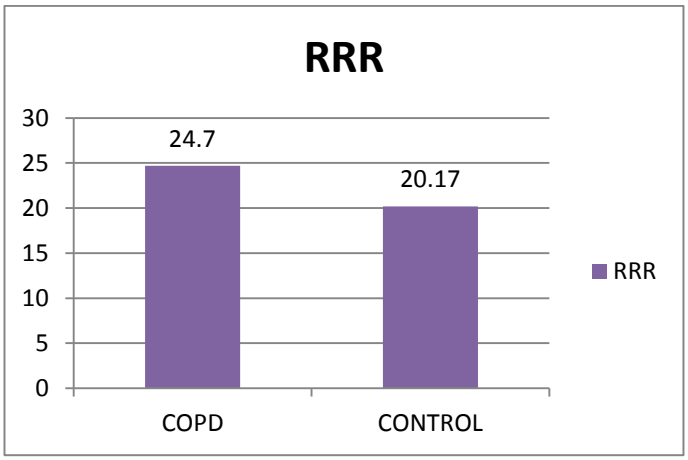


CHART NO 6-7 RRR AND BLAR

	COPD	CONTROL
RRR	24.7	20.17



	COPD	CONTROL
BLAR	2.38	2.5

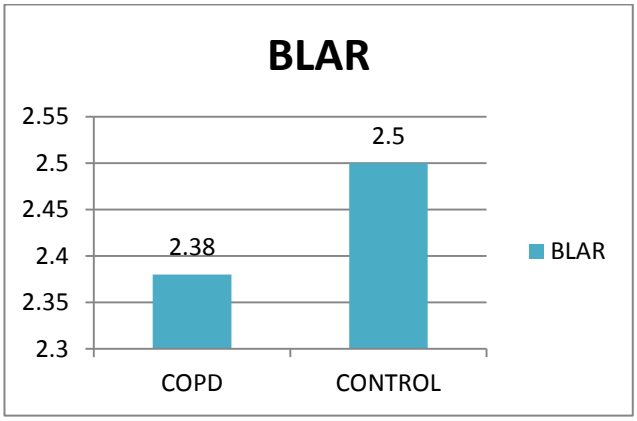
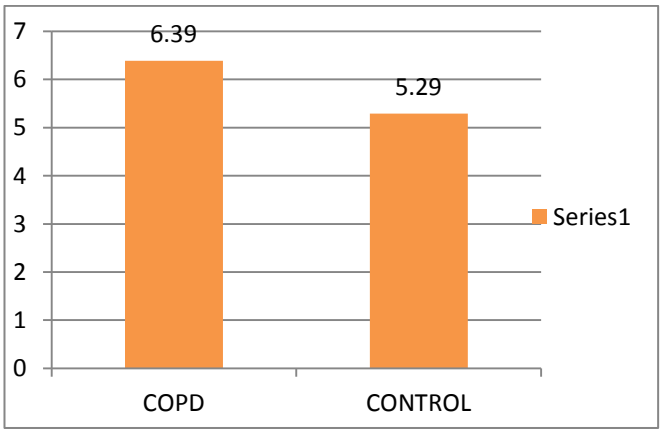


CHART NO 8-9 BLA1 AND BLA2

	COPD	CONTROL
BLA1	6.339	5.29



	COPD	CONTROL
BLA2	5.15	4.26

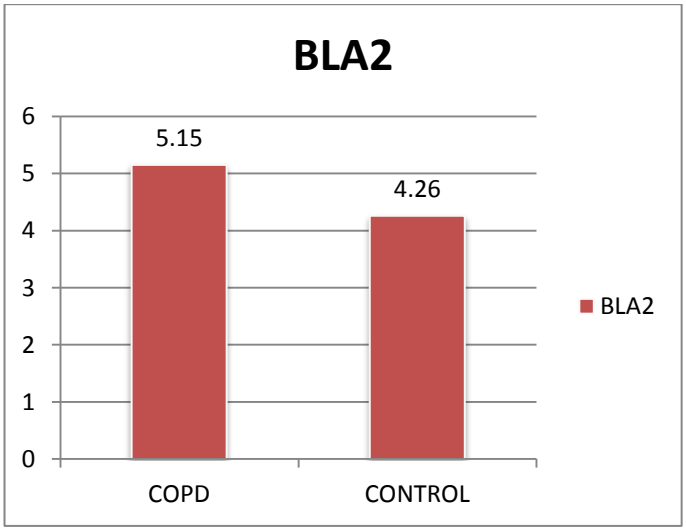


CHART NO 10 BLA3

	COPD	CONTROL
BLA3	2.85	2.49

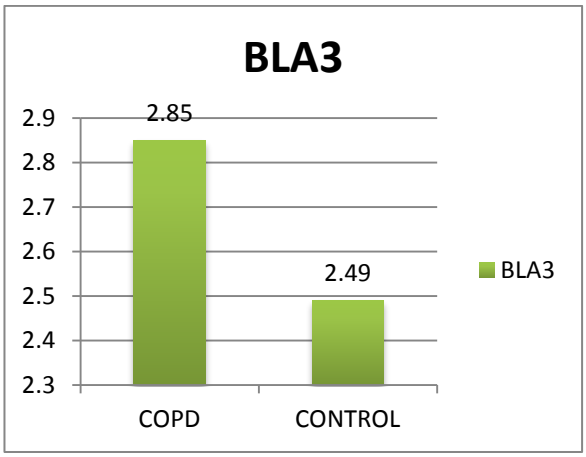
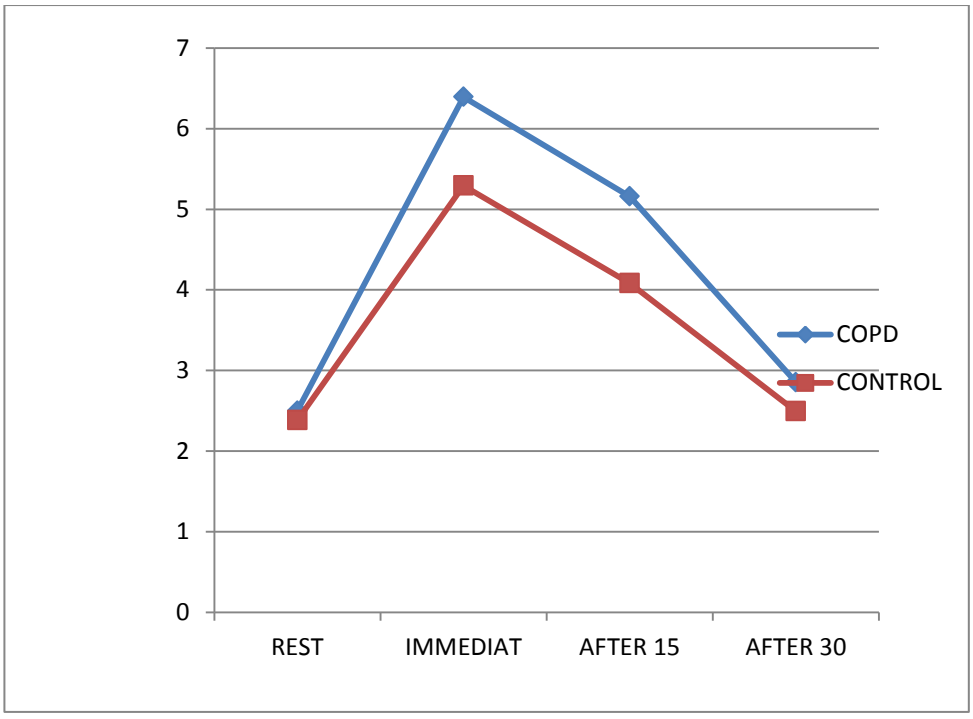


CHART NO 11

PRODUCTION & RECOVERY RATE OF LACTATE

	REST	IMMEDIAT	AFTER 15	AFTER 30
COPD	2.5	6.394117647	5.15882	2.85294
CONTROL	2.382352941	5.294117647	4.08235	2.49412



STATISTICAL ANALYSIS

COPD GROUP AND ITS DATA

No	FEV1% of predicted	FVC % of predicted	FEV1/FVC % of predicted
AVERAGE	50.17	64.05	0.77
SD	17.16	19.38	0.06
T	8.70441E-08	0.02	3.07392E-10
	SIGNIFICANT	SIGNIFICANT	SIGNIFICANT

NO	HRR	SBPR	DBPR
AVERAGE	92.58	130	83.52
SD	11.41	11.95	7.52
T	0.01	0.49	0.35
	SIGNIFICANT		

NO	BLAR	BLA1	BLA2	BLA3
AVERAGE	2.5	6.39	5.15	2.85
SD	1.00	1.68	1.53	1.18
T	0.72	0.06	0.065	0.33

NO	SPO2R	SPO_21	RRR
AVERAGE	96.35	92.47	24.70
SD	2.78	2.40	4.90
T	0.35	0.014	0.003
		SIGNIFICANT	SIGNIFICANT

CONTROL GROUP AND ITS DATA

NO	FEV1% of predicted	FVC % of predicted	FEV1/FVC % of predicted
AVERAGE	95.29	81.70	1.19
SD	20.57	23.57	0.14

NO	HRR	HR1	RRR
AVERAGE	80.94	124.11	20.17
SD	14.78	9.51	2.98

NO	BLAR	BLA1	BLA2	BLA3
AVERAGE	2.38	5.29	4.08	2.49
SD	0.95	1.68	1.74	0.91

NO	SPO2R	SPO21
AVERAGE	97.29	94.82
SD	3.01	2.89

NO	SBPR	DBPR
AVERAGE	127.41	81.35
SD	9.91	5.77

Anova: Single Factor

SUMMARY						
Groups	***Count***	***Sum***	***Average***	***Variance***		
BLAR	17	40.5	2.382353	0.907794		
BLA1	17	90	5.294118	2.851838		
BLA2	17	69.4	4.082353	3.037794		
BLA3	17	42.4	2.494118	0.845588		
ANOVA						
Source of Variation	***SS***	***df***	***MS***	***F***	***P-value***	***F crit***
Between Groups	98.64985	3	32.88328	17.20959	2.65E08	2.748191
Within Groups	122.2882	64	1.910754			
Total	220.9381	67				

RESULT

17 patients with COPD and 17 normal individual were enrolled for this study. The detail anthropometric data and other necessary information are given in the below chart. The criteria of GOLD classification were adopted for the COPD patients.

As per the result there is small rise in RR, SBP, and DBP in COPD patients as compare to the normal individuals. There is no significant difference in resting blood lactate level between COPD and normal individuals.

There is a significant difference in FEV_1, FVC and FEV_1/FVC between COPD and control group. This is because COPD is an obstructive lung disorder which gives reduced FEV_1 and FEV_1/FVC.

Blood lactate level at rest, immediately after exercise, after 15 and 30 minutes of exercise are shown in the chart, which suggests that blood lactate level is increased in both the group immediately after exercise but the increment is more in COPD group of patients compared to the control group. Once the exercise is stopped and again blood lactate is measured after 15 minutes, in both the group blood lactate level is reducing but still it was higher than the baseline level, after 30 minutes of exercise the blood lactate level is almost reached to the baseline level. The lactate level is increasing in both the group but it is increasing more in COPD group than the control group significantly.

Heart rate immediately after an exercise is significantly more in COPD group compared to the control group. The difference between saturation in both the group was not significant at rest but after an exercise there is significant difference between COPD and control group with respect to the blood saturation.

DISCUSSION

Patients with COPD may develop high ventilatory and metabolic output when they perform simple household activity in routine base. Impaired exercise tolerance is a prominent complaint of patients with obstructive lung disease. Unlike healthy subjects, patients with obstructive lung disease are often limited in their exercise tolerance by the level of ventilation they are able to sustain .Improving physical performance is an important therapeutic goal in COPD. Recent evidence has said that muscle mitochondrial (oxidative) capacity is reduced and that may be the reason for the exercise intolerance in this population. [60] [61] [58].One of the important factor that has an effects on exercise ventilation is CO_2 production which is generated by aerobic metabolism and buffering of lactic acid, which is formed an aerobically when oxygen demand exceeds supply to exercising muscles. [61]

Lactate production is a natural process and it is produced even at rest and it is removed also, but when the production rate is increased more than removal it is accumulated, or the removal of lactate is done by the heart, kidney, liver and non exercising muscle.

The increase in blood lactate level during the progressive exercise is the interest of many physician, clinician, sports coaches and many researchers in today's new era. Lactate is the marker of peripheral muscle anaerobic metabolism and fatigue. [62]. The blood lactate response to exercise has interested physiologists for over many years, but has more recently become as routine a variable to measure in many exercise laboratories as is heart rate. This rising popularity is probably due to: a) the ease of sampling and improved accuracy afforded by recently developed micro-assay methods and/or automated lactate analyzers; and b) the predictive and evaluative power associated with the lactate response to exercise. Several studies suggest that the strong relationship between exercise performance and lactate-related variables can be attributed to a reflection by lactate during exercise of not only the functional capacity of the central circulatory apparati to transport oxygen to exercising muscles, but also the peripheral capacity of the musculature to utilize this oxygen. [63]

The precise mechanism by which blood-lactate accumulation occurs during exercise comprises many factors like the mass of exercising muscle, supply of oxygen to that muscle in blood, diffusion into cells, and the efficiency of utilization by those muscle cells. [64]

The production of more lactate is one of the primary factors for the limitation of the exercise performance in the COPD patients. Our result confirms that lactic acid production is increased as the level and stress of exercise is increasing, but there is no significant difference in increment level between COPD and control group with respect to the production and recovery of the lactate.

This study has some limitation like sample size should be more, we have not categorized the severity of COPD patients and we did not compare the lactate production and recovery in different group of the COPD patients. We did not measure the lactate production at the maximal cardiopulmonary exercise level as it was not the purpose of this study. In the current study the other parameters like blood pressure and oxygen saturation is measured only at rest and not immediately after exercise, after 15 and 30 minutes of an exercise as the primary concern was just to measure the rate of production and recovery of lactate.

In our study the lactate production is more in the COPD patients, as in COPD patients the oxygen supply to the body is limited or reduced as compared to the other normal individual so during exercise as the oxygen supply is reduced the exercise shift towards the anaerobic metabolism and the end product of anaerobic metabolism is pyruvate which

converts into lactate and this increases the production of lactate in COPD patients compared to the normal individual so anaerobic metabolism break down the glycogen leads to an accumulation of inorganic acid that is lactic acid, as lactic acid is a very strong acid it immediately converts into lactate and hydrogen ion which indirectly causes fatigue in many COPD patients and this is supported by the study done by Hakan westerblad in 2002. [65]

In COPD patients the respiratory rate is increased more which leads to less time for the expiration and causes dynamic hyperinflation which is the main cause of respiratory discomfort and exercise limitation. [66]

Katz and Sahlin [67] had collected data and postulates that lactate production is O_2 dependent .In fact they said that when O_2 supply is less or limited then mitochondrial respiration is begin by increase in ATP and Pi (inorganic phosphate) and the reduced form of NADH (nicotinamide adenine dinucleotide).This favors the stimulation of glycolysis, which will increases cytosolic NADH formation which will shift the lactate dehydrogenase (LDH) equilibrium toward increase lactate production. They propose that oxygen supply plays the most important factor in lactate production.

In 1996 F Maltais and et al done a study on COPD subjects and each subject performed a stepwise exercise test on an ergo cycle up to their maximum limit and they concluded that lactic acid rises steeply in COPD group and they said that the activity of the oxidative enzymes (citrate synthase CS, and 3-hydroxyacyl CoA dehydrogenase HADH) was significantly lower in COPD than in control group so this study also supports our study results. [12]

F Maltais , A A Simard and et al in 1996 suggested that in COPD group compared to the normal group, the increment in lactate production is steeper in COPD group, they said that reason for this is the activity of the oxidative enzymes was significantly lower in COPD groups than the control subjects. They have also found no difference in glycolytic enzymes. They concluded that oxidative capacity of the skeletal muscle is reduced, and increase in arterial lactate during exercise is excessive, and these both results are interrelated. [12]

In our study the increase in heart rate, respiratory rate, and systolic blood pressure is the response of exercise in both the group. But resting heart rate and respiratory rate in COPD group is significantly higher than the control group. The reason for this is that the impairment in COPD brings to the pulmonary mechanism which can leads to the decrease venous return and ultimately leads to increase heart rate at rest, and because of this there is higher blood pressure at rest compared to the normal individuals. In this way COPD can affect the heart

rate at rest also and this is a very important factor as it decreases the reserve heart rate available for any kind of exercise/efforts. [68]

In our study results suggest that lactate is increasing in both the group significantly when they perform sub maximal level of exercise but the increment of lactate is more in the COPD group which suggests that COPD patient gets fatigue early and easily as lactate production is increased more than the control group at sub maximal exercise level, this is very interesting as well as important as our routine day to day activity involves sub maximal exercise and that might be the reason that COPD patient either don't perform the routine activity or if they perform these activity they gets fatigue very easily and which turns them into avoidance of these activity which deteriorates their functional ability and capacity to perform the routine task.

The respiratory rate is more at rest in the COPD group than the control group, because the hydrogen ion which is produced by the dissociation of the lactic acid into lactate and hydrogen ion with the help of bicarbonate and converts to produce CO_2 and this increases the load onto patient. Moreover the hydrogen ion itself is the stimulus for the ventilatory drive .Both the increased in CO_2 generated by buffering and the respiratory stimulation by the hydrogen ion are perceived by the patient as breathing stimuli and which increases the respiratory rate. [11]

The occurrence of metabolic acidosis in patients with COPD during exercise may be crucial for the designing the proper rehabilitation protocol. For example in patents in which develop the metabolic acidosis, exercise training has the some potential to improve exercise tolerance. Reduction of metabolic acidosis translates into ventilatory requirements and the same amounts of exercise can be performed with less ventilation which also reduces the dyspnoea.

Immediately after an exercise there is more increment of heart rate in the COPD group than the control group which suggests that in mild to moderate activity like in our study (sub maximal exercise) also increment of heart rate is more in COPD group. The explanation for this is again as like how heart rate is more in COPD group at rest, same way the heart rate immediately after an exercise is more in COPD group. As the level of exercise increases the oxygen and other nutrient material are more required to the working muscle and in COPD group the oxygen supply is less because of the obstruction which is compensated by more increment in the heart rate compared to the control group after a sub maximal exercise.

The lactate level is not significantly different in both the group at resting level. The lactate level is increasing in both the group immediately after an exercise, 15 and 30 minutes

of an exercise but the level of increment is higher in COPD group compared to the control group at the sub maximal level of exercise. We have not allowed any person from both the group to reach at the maximal level of exercise as it was not the aim of my study. The level or stress of the exercise was measured by the PRE at each minute of the exercise and at end of 5 minutes the PRE of both the group was somewhat hard to hard.

The reason why I have not chosen the maximal level of exercise is that in routine, day to day activity mostly occurs in the sub maximal level of stress and what is the lactate level during sub maximal level of an exercise.

So the finding of lactate production in patients with COPD may prove to be useful in deciding whether to include exercise training as part of an individual's rehabilitation program. [11] [69]

CONCLUSION AND FURURE DIRECTIONS

The overall prevalence of COPD in India and in other countries in increasing day by day despite profound research in COPD.

As COPD not only affects respiratory system but it also affects the other system in our body, it is not confined only to the lungs but it is a multisystem manifestations. So it is very important to understand the effects of exercise and its response to the COPD patients which is done by this study with respect to the production of lactate and its recovery rate in COPD patients.

The physiological change which is associated with the lactate production and accumulation has significant influence on the cardiopulmonary performances. The lactate accumulation leads to hyperventilation, altered oxygen kinetics and impaired muscle performances in any individual. Thus it is very important to find out any early lactate accumulation in COPD or any normal individual and accordingly some kind of intervention can be given to reduce or to delay the lactate accumulation during exercise.

In conclusion the COPD group not only generates high concentration of blood lactate similar to those observed in normal controls at sub maximal level of exercise but also this occurs earlier than the normal group. The recovery rate is almost similar in both the group. Measurement of the lactate threshold is a very useful way of assessing fitness and the response to intervention, such as exercise training.

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