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CONTENT

EDITORIAL

Medical Science & Care : Let it be an "inclusive" growth for India

Physicians in this part of the world have to work in an altogether different ground reality than those working in the developed world as far as the practice of the so called 'modern medicine' is concerned. It is necessary for practitioners and as well the scientists here to recognize the principles, the spirit of evidence based approach of the medical sciences, and accept the valid scientific developments with open and rational mind. But it often turns pathetic when we forget the ground reality of our soil and act, being proud at times, to translate the western teaching without modification apt for application on our soil. This statement includes almost every area of our practice of medicine in the country starting from investigating a patient, prescribing medicines, evaluating a scientific experience, an even in dealing with the medico-legal issues. Unfortunately, somewhat line to line copying of the western models has turned a matter of pride and yard mark of efficiency. Those so called 'fortunate' or 'unfortunate' members working in tertiary care set ups often feel themselves responsible to safeguard the sanctity of the western guidelines and do not feel it worthwhile to try to understand the actual reality at the grass root. Unfortunately, this so called 'elite' class of the Indian physicians remain the face of the nation and they often pose (and perhaps feel too) as the 'stockholder' of the Indian medical research and healthcare.

Despite poverty and utter lack of basic healthcare facilities in many situations, there are 'state of the art' hospitals, proud corporate infrastructures beaconing health tourists, and highly academic tertiary care public sector institutes in the country. Within the 'world' named India, there are many smaller 'worlds' with difference in size, shape, quality, corruptions, aspirations, and many other variables that makes the Indian healthcare a distinct and unique mosaic of facts and figures. The problem and the potentials of this lattice look and unique have been tremendous but unfortunately the key stockholders often appear 'skewed' in their vision and actions. It is not expected that the things will change overnight but it is expected that the change will come as an 'inclusive' one where the real world will get proper importance in our mindset. This need a nationalistic attitude and outlook which will help us to assimilate the knowledge and developments of modern medicine as an important media to provide health care to over a billion of our countrymen than just translating the science in practice and academics as photocopying the western style forgetting the reality and strength of ours.

We need to look at our positive side too, need to recognize even the smallest of our efforts and innovations, give more value to the scientific work which has an immediate impact on our healthcare than those been just proud of 'impact factor' issues of publications without any help to add value to real life. In medical care too, as in technology, we need to look more at our own, at indigenization, identifying novel observations, making use of technology to solve our problems, and overall feeling great to develop our own modus-operendi that will be flexible, easy to apply, and effective as well. Let us, at all level of functioning, not feel ashamed for what do not have; rather be bold to face the reality and try to find the ways of solution of our problems. Perhaps, we can do far better despite our limitations; let us change the weaknesses to strength.

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LATERAL THINKING

New science of man Man, the known

Human body is a colony of 50 trillion happy individual human cells, each of whom existed as single organism for millions of years during evolution to have come together lately for economic reasons. When all of them are in synch, one is healthy and vice versa. In addition, the human body consists of trillions of germs living in symbiosis with man having been incorporated into his genome-together called human metagenome having about 25,000 human genes and 2-3 trillion germ genes.

Every human cell has its own mind in its cell wall, called

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memBrain. The cell is capable of all functions that the whole human body is capable of. However, evolutionary economics did teach the cells that it is easier to delegate powers to groups of them with a specific task, instead of each of them doing all the jobs all the time. That is the birth of morphologically different cells in different parts of the body called organs, but they all function the same way for doing their assigned tasks. They have different shapes but work identically.

Each one of us is a part of this macrocosm and, is, interconnected. Therefore, our cells also vibrate in consonance with cells of other organisms and even plants. In short, everything in this universe is related. One of the important hitherto unknown risk factors for illness is hurting others. Scientifically, hurting others is like hurting ones' own body parts; a kind of *social autoimmune disease*!

When we realize this oneness, otherwise called *aduality* in quantum physics, the egoistic "I" concept changes to the altruistic "We" concept. The relevance of modern physics to medicine can be gauged from the following.

"Quantum theory is such a wonderful example of a situation that one can understand something in complete clarity and at the same time realizes that one can only talk about it in terms of images and metaphors."

Werner Heisenberg
In Der Teil und das Ganze- (Physics and Beyond).

JC Bose, Indian physicist had hinted at the possibility of human, animal and plant consciousness. Russian medical scientist, Professor Alexander G.Gurvich in 1923 recorded the presence of "mitogenic rays" from human cells. By 1930s this information reached Europe and researchers both there and the USA have been looking for such rays. It was in the year 1974, German biophysicist, Fritz-Albert Popp had proved their existence, their origin from the DNA and, later their coherence (laser-like nature), and had developed biophoton theory to explain their possible "biological role and the ways in which they may control biochemical processes, growth, differentiation."

Popp's biophoton theory leads to so many new insights into the life processes and may provide key to the major elements of a future theory of whole person healing based on such an approach. The importance of the discovery has been confirmed by eminent scientists such as Herbert Froehlich and Nobel laureate Ilya Prigogine. The International Institute of Biophysics, a network of research laboratories in more than 10 countries, based in Germany, is coordinating research in this field. "The holographic biophoton field of the brain and the nervous system, and maybe even that of the whole organism, may also be basis of memory and other phenomena of consciousness, as postulated by neurophysiologist Karl Pribram and others. The consciousness-like coherence properties of the biophoton field are closely related to its base in the properties of the physical vacuum and indicate its possible role as an interface to the non-physical realms of mind, psyche and consciousness," writes Marco Bischof in his book Bio-Photons-the light of our cells.

Recent work of physicists like William Tiller, Hans Peter Duerr, Joie Jones and material scientists like Rustum Roy we have been able to unravel the mystery of human physiology to a large extent. Indian Ayurveda's holistic model comes very close to an ideal model. In view of the advances in quantum mechanics, we might have to fine tune that model slightly to be perfect. Work is going on in that direction. Human body is a bundle of jumping lepto-quarks. (Subtlest energy particles at the subatomic level where matter and energy have no difference) Although we all look solid and distinct, there is nothing solid about us. Because there is no difference between energy and matter, the delusion of solidity has been mistaken for reality.

When Popp applied an ointment on the hand, the photon lights changed even in distant brain or leg! Body cells do communicate with one another and try and help each other. The photon light could even make the photon lights from others to vibrate in communion with ours showing thereby that we are all interlinked through the universal consciousness. Health was defined by Popp as that state where our body cells are in sync with each other. Illness is a state where the cells are out of sync. In fact, each one of our body cells loves another cell not only in our own body but even in others' bodies. But for the immune system provided by nature, we would all have become a large syncitium. Imagine a situation where on the one hand our body cells love another person's body cells and our mind hates that person, there will be a conflict with the "me-you" concept which might result in autoimmunity! Recent epidemiological studies have shown that anger, jealousy, hostility and frustration with depression are very potent risk factors for killer diseases.

Post modern medicine; the future:

If the body is the mind and the body cells are only energy vibrations the future medical care, which I call as post-modern medicine or meta-medicine, has to be holistic and energy based. Disease being energy based its healing must also be based on energy. We have been working in this field for fifteen years with significant success. Health, then, loses its present reductionist connotation of absence of physical organ based diagnosis. On the contrary diseases are but altered energy pattern of the human body which needs resetting the altered energy pattern using energy from outside. There is now recognition for a new word "Whole Person Healing" or WPH as the future. This was introduced by Late Professor Rustum Roy and was accepted by the IOM (Institute of Medicine) in 2010. Consequently health gets a new definition. *It is enthusiasm to work and enthusiasm to be compassionate.*

With these newer insights the time honored organ based disease screening, setting the aberrations right with hi-tech quick fixes and reductionist chemical molecules become redundant. Mankind has been experimenting with this kind of medicine for eons in our ancient cultures all over the world. Although observational longitudinal research has given credence to them, we need to authenticate them using the hard scientific yardsticks which work we have been doing in our World Academy of Authentic Healing Sciences for well over a decade. We need to do more before this becomes common practice. Still we would need emergency trauma care and surgical corrections to be retained from the present modern medical systems with innovations to fit the new paradigm. We can not throw the bath tub and the baby together just because the bath water is dirty.

This combination of the new and old should be the future of human illness management. In addition to the known three energies in sciences we might have to make use of the occult energies which our ancestors have harnessed to heal mankind like Yoga, meditation, Ayurveda, Chinese Chi, praanic healing and many such. Each one of them needs to be re-authenticated using today's modern scientific methods before being incorporated into the post-modern medicine.

ORIGINAL RESEARCH

Group III Pulmonary Hypertension: relative frequency of different etiologies in a referral pulmonary OPD

Abstract:

Background: the prevalence of Pulmonary Hypertension (PH) is unknown in India and very few sketchy data are available. The diagnosis is mainly done by referral centers.

Method: All the consecutive patients being diagnosed as PH (group III) (based on a novel clinic-radio-echocardiographic criteria) in our outpatient services over a defined period were recorded and included according to the underlying etiology through a logical and feasible algorithm of evaluation followed at the institute. Patients with clear-cut diagnosis of COPD, asthma, DPLD, OSA and CTEPH were charted along with those having no other obvious etiology but history of treatment of tuberculosis in the past, and another group marked as 'others' consisting of some known (sarcoidosis, chronic liver disease etc) and some yet not completely evaluated patients.

Results: Out of 1521 patients attending the OPD during 1st January, 2013 to 30th June, 152 (9.99%) patients were diagnosed to have PH. On etiological classification, the relative frequency has been 35.53%, 7.89%, 14.47% and 7.24% for COPD, asthma, ILD, OSA with CTEPH together. The patients with history of tuberculosis without any other apparent etiology formed 9.87% and the 'other' group consisted of 25% of the total PH patients.

Conclusion: The presence of Group III PH is not infrequent in pulmonary practice in our part of India and the association of tuberculosis with PH appears to be important and demands further evaluation.

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Introduction: The Dana point classification of PH and subsequent guidelines describes Group III PH to develop from chronic lung diseases and sleep apnoea [1, 2]. To our experience, the condition, though not infrequent, has been escaping detection probably out of lethargy and lack of awareness been prevailing amongst pulmonologists in this country which is largely because of non feasibility of the diagnostic modalities (especially the right heart catheterization) and the non availability of effective and easily administrable anti PH therapy in India till the recent past. In short of RHC we have developed easy and feasible composite criteria on clinic-radio-echocardiographic parameters to detect PH [3] and tried to see the prevalence of PH in our outpatient attendees over a defined period. Further, we tried to see the common etiologies involved in our patients based on an algorithm been used to diagnose them. Here, we present the result of our effort in terms of understanding the load of Group III PH to our OPD and appreciating the peculiarities of each group based on the available variables.

Methods: We look for the number of patients diagnosed to have PH in our OPD from the record of the institute from 17th December, 2012 to 12th August, 2013. The diagnostic criteria for PH included at least one positive feature from each of the three groups as a) clinical symptoms, b) radiological abnormalities, c) Doppler Echo-cardiographic determination of systolic pulmonary artery pressure more than 40 mm of Hg. **The clinical criteria** included the detection of an unexplained SOB or disproportionate SOB with demonstration of hypoxemia (either the resting baseline less than 94 %) or desaturation a drop in arterial oxygen saturation = 3 % (with a mild and defined exercise of walking = 15 meters in the consultation office) with or without the presence of other symptoms as unexplained fatigue, syncope etc. **The radiological criteria** happened to be a) the **Chest x-ray showing wide** main pulmonary arteries (increases diameter) at right or left hilum and / or gross PA dilatation / fullness of pulmonary bay with or without radiological suggestion of right ventricular enlargement with **HRCT Chest showing either pulmonary artery trunk** diameter = aortic root diameter or /and pulmonary artery branch diameter = accompany bronchial diameter in three or more lobes. The **Eco cardiograph with doppler and tissue Doppler criteria included** a) PA systolic pressure = 40 mm of Hg. Our basic intension was to diagnose symptomatic patients with PH with reasonable certainty without the knowledge of the exact PA pressure that need right heart catheterization.

Simultaneous to this, the diagnosis of the underlying etiology was attempted with appropriate investigations according to a practical algorithm been followed in the institute. Alongside the evaluation for PH the investigations (chest x-ray, HRCT chest, and echocardiography done by a single echocardiographist on a defined protocol), the patients were evaluated for the establishment of the etiological diagnosis through spirometry for all, ventilation scan or CT pulmonary angiography for suspected thromboembolic pulmonary hypertension, sleep study with suspicion of OSA, bronchoscopy with TBLB for suspicion of diagnosis of sarcoidosis, collagen profile and other tests in other suspected etiological situations. Thus, etiologically diagnosed patients were further sub divided according to the primary diagnosis and charted under six groups as a) COPD, b) ILD / DPLD, c) asthma, d) PH with history of tuberculosis, e) OSA and CTEPH (without parenchymal or airway disease diagnosis), and f) 'others' where the diagnostic workup has yet been incomplete or not possible to extent needed, or has not yielded any etiological clue (possible PAH). This last group may included sarcoidosis, other restrictive diseases, PAH, and other causes of PH. All the patients had an assessment of the health status in terms of CAT score (COPD assessment test) at the time of presentation.

Results: A total of 152 patients (Male 100, female 52) were diagnosed to have presence of PH in our OPD during the period. The distribution of the patients with demographic, lung function, oxygen saturation at rest, Doppler echocardiography determined PA pressure, and health status in terms of CAT score are charted in Table – 1.

Table – 1

	COPD	ILD	Asthma	History of TB	OSA and CTEPH	Others
Total no of patients seen	227 (14.92 %)	107 (7.03 %)	680 (44.71 %)			
Total Number of patients with PH	54 (23.79 %)	22 (20.56 %)	12 (1.76 %)	15	11	38
M:F ratio	49:5	10:12	7:5	6:9	6:5	20:18
Mean Age	66.65 ± 7.43	59.18 ± 11.15	58.75 ± 13.59	57.2 ± 13.92	62.64 ± 13.05	59.92 ± 11.77
Mean BMI	21.78 ± 4.18	24.87 ± 4.68	28.1 ± 2.50	21.77 ± 3.93	35.1 ± 7.75	29.14 ± 4.90
Mean SaO2 (at rest)	93.84 ± 6.94	92.95 ± 4.42	95.67 ± 2.27	91 ± 6.19	93.67 ± 2.42	95.41 ± 3.13
Mean Pulse Rate (rest)	89 ± 15.23	99.4 ± 19.61	89.08 ± 16.70	105.38 ± 16.23	85.5 ± 8.24	94.23 ± 13.22
Mean Smoking Index	587.18 ± 392.73 (n = 44)	364 ± 263.68 (n = 6)	466.67 ± 538.80 (n = 6)	455 ± 398.13 (n = 7)		370.63 ± 357.81 (n = 16)
Mean (%) FVC	60.17 ± 20.25	48.5 ± 20.09	55.44 ± 10.71	49.9 ± 16.13	74.25 ± 29.69	67.45 ± 16.37
Mean (%) FEV1	40.05 ± 18.19	51.7 ± 17.37	44.53 ± 14.72	41.6 ± 18.01	79.5 ± 34.58	67.7 ± 15.02
Mean FEV1/FVC	51.75 ± 12.17	90.33 ± 10.68	65.02 ± 17.87	67.67 ± 20.57	82.88 ± 9.86	82.63 ± 7.65
Mean (%) FEF_{25-75}	15.77 ± 8.87	81.2 ± 28.48	29.07 ± 20.13	40.9 ± 43.07	78.5 ± 49.14	53.49 ± 22.50
Mean PA Pressure (systolic)	45.32 ± 9.52	51.2 ± 10.7	42 ± 3.50	45.57 ± 11.86	43.75 ± 6.94	48.2 ± 8.73
Mean CAT score	15.87 ± 5.53	19.28 ± 5.42	15.55 ± 6.07	17.08 ± 5.38	17.27 ± 6.69	15.63 ± 6.96

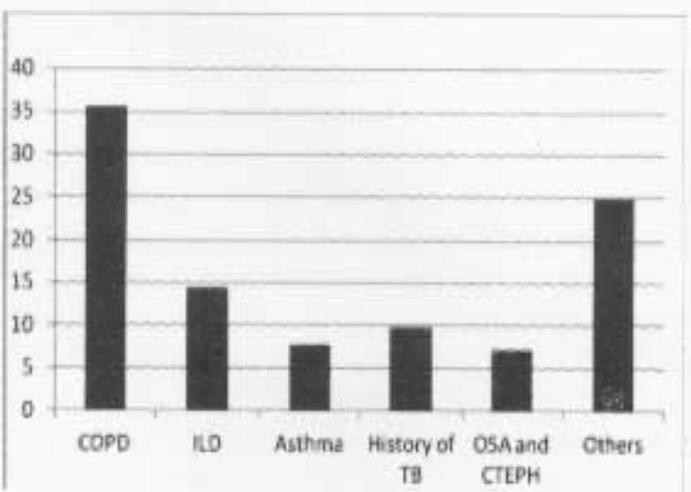

Figure 1: presents the relative % of PH patients with different etiologies attending IPCR

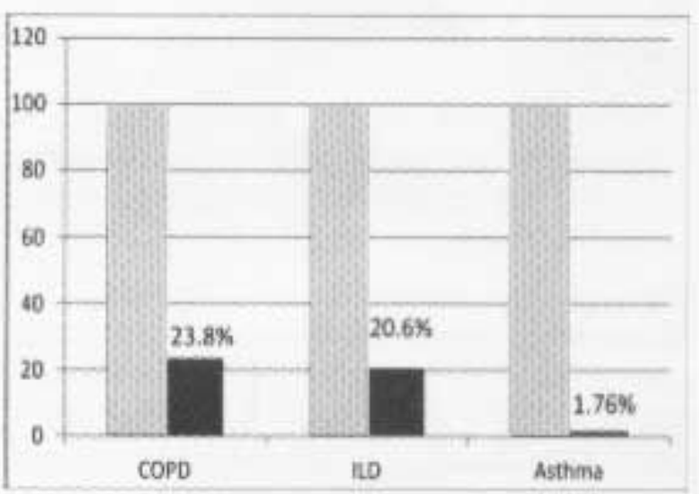

Figure 2: presents the relative prevalence of PH in COPD, ILD and Asthma

Discussion: Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest, as measured by right heart catheterization [4]. Group- III PH is often encountered by pulmonologists and several lung disorders as COPD, ILD, and OSA etc are known to cause PH and corpulmonale in course of time. Here, our observation shows some interesting facts as a) COPD, asthma and ILD form 35.53%, 7.89%, 14.47% of our patients with PH, b) history of tuberculosis, though not well reported so far in literature, has been associated with 9.87% of the PH patients in our experience while c) OSA, CTEPH form a smaller percentage (7.24%) of the PH patients. Such etiological classification of PH in attending patients to referral pulmonary hypertension clinic has been recorded [5] but possibly none been published from a referral general pulmonary practice. There have been documented regional differences in the frequencies of different etiologies for PH in different parts of the world [6, 7, 8] and without a PH registry been available in India, it is not possible to compare to that of any. Thus, our work can just act as a sensitizer for the need of one such in the country.

To our mind, the basic hindrance to do such job remains at the logistics of practicing right heart catheterization. Given the fact that criteria based on CT scan of chest can have very high predictive power to diagnose PH (PA pressure been taken as 20 mm as the cut off) [9, 10], it is likely that the composite criteria (that includes the CT features been considered) chosen by us can diagnose the presence of pulmonary hypertension (with PA pressure cut off value being 25 mm of Hg to define PH) more predictably although the exact value of the PA pressure cannot be measured or commented upon. Therefore, as the diagnosis of PH is unquestionable in our workup system, such etiological assessment of PH should remain valid scientifically.

The observation reveals some interesting findings. The lowest mean age was for those with history of tuberculosis (57.2 ± 13.92 years) but they had the mean lowest BMI (21.77 ± 3.93) and the lowest mean arterial oxygen saturation (91 ± 6.19 %) at rest with highest mean pulse rate (105.38 ± 16.23) and PA pressure (systolic PA pressure as 45.57 ± 11.86 mm of Hg) highest amongst the different groups suggesting that these people have probably a higher degree of systemic inflammation and endothelial dysfunction. Such PH has been reported in treated patients of tuberculosis in Sudan where the patients presented with shortness of breath after an average of 9 years of treatment [11]; the association needs further study and recognition. Another interesting and noteworthy finding is the PH in asthmatics which is also not well recognized as the literature remains scanty on this area [12]; incidentally all our asthma patients had severe airflow limitations suggesting chronic disease and we did not seriously look for co-presence of other contributing causes. This area too needs further probing.

As per the BMI has been concerned, the group with OSA and CTEPH (group IV PH) have the highest value (35.1 ± 7.75) and COPD remains the close contender with those with history of tuberculosis for the lowest with a value of 21.78 ± 4.18. The prevalence of smoking has been highest in COPD while the mean smoking index in the smoker population of different groups shows that COPD again tops the list with a figure of over 500. PH in COPD is well known and fairly well studied [13, 14]. All our patients (mean FEV1 40.05 ± 18.19) belong to the common type of COPD PH association where the PH is mild to moderate with advanced COPD [15]. Lung function wise ILD, patients with OSA and CTEPH, and the patients of the 'other' or the indeterminate group show evidence of restriction, the degree of which was most severe in the ILD patients with % FVC as 48.5 ± 20.09 while that was mild in the last group ('other' diseases) and was near normal in patients with OSA and CTEPH (74.25 %). The other three category of patients as COPD, patients with history of tuberculosis, and asthma had feature of airflow obstruction in their spirometry. Incidentally, all the three groups had features of severe obstruction with % FEV1 falling less than 50. Lung function wise the patients with history of tuberculosis show obstructive changes akin to that of COPD population and if the history of the disease has been omitted, one could have grouped them in COPD only. This supports the concept that tuberculosis can cause COPD [15, 17, 18]. Interestingly, when the so called marker of the small airway obstruction (FEF_{25-75}) has been considered for comparison, the COPD group has the worst percentage as 15.77 ± 8.87 followed by asthma and patients with history of TB as 29.07 ± 20.13 and 40.9 ± 43-07 respectively suggesting that the small airway affection in patients of PH with history of tuberculosis appears unlikely and these patients have a

peculiar kind of airway obstruction which does not fit to that with asthma or COPD. Further subgroup analysis of these patients based on history of smoking may make us wise on such issues. Health status wise asthmatics and the COPD sufferers had the poorest status followed by those with history of tuberculosis. For convenience, we have adopted CAT score for assessing the health status of all the different types of patients. CAT has been a well accepted validated tool for the assessment of COPD [19, 20] and has also been applied to DPLD [21]. Its use in cases of PH or any other types of lung disease, though looks rational, has not been validated so far. This instrument has been used for its simplicity in application and for maintaining uniformity of assessment in all the categories as the components of CAT applies very well to all such patients with non COPD pathology. The association of PH in DPLD has been well known [22, 23].

There are several rooms for criticism in this study. The diagnosis of PH, although established to our opinion, was not supported by the right heart catheterization, the 'gold standard' for the diagnosis of PH. Naturally, we cannot state the exact PA pressure based on echocardiographic value as echocardiography has several limitations [24]. The relative frequency of PH in our study actually presents the situation in a tertiary pulmonary OPD; it has very limited epidemiological value. The validity of CAT score beyond COPD and DPLD has not been tested so far. Finally, the observation leaves us with many questions and makes us aware to look more methodically for Group-III PH in practice. This may mean helping the quality of life to a large number of patients with Group-III PH in our community.

Abbreviations:

PH – pulmonary hypertension
PAH- pulmonary artery hypertension
OPD – out patient department
IPCR – Institute of Pulmocare & Research
COPD – chronic obstructive pulmonary disease
ILD – interstitial lung disease
OSA – obstructive sleep apnea
CTEPH - chronic thromboembolic pulmonary hypertension
PAH – pulmonary arterial hypertension
RHC – right heart catheterization
SOB – shortness of breath
PA – pulmonary artery
AO – aorta
CAT – COPD Assessment Test

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ARTICLES

Clinical Trials- Recent Regulatory Changes

Clinical trials in simple words mean any investigation on human subjects carried out by pharmaceutical companies, Investigators, research institutions in order to discover or verify the clinical and pharmacological effects of any investigational medicinal product(s) and/or to identify any adverse reactions of such medicinal products(s) and/or to study such investigational medicinal product(s) with the object of determining its safety and/or efficacy

In addition to national laws, clinical trials are governed by well established guidelines and regulations like EU regulations and directives, ICH- Good Clinical Practices (GCP) guidelines, recommendations of World Medical Association Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practices and ICMR guidelines.

These guidelines mainly aim at protecting the subject from taking undue risk in participating in a clinical trial; apply voluntary consent to research and the routine assessment of risk and benefit. In India, Central Drugs Standard Control Organization (CDSCO) (headed by Director Control General of India) is the primary authority and "Drugs and Cosmetics Act, 1940" is the principal legislation for the regulation of clinical trials. Schedule Y of the Drugs and Cosmetics Rules, 1945 ("Rules") provides for the detailed settings, and compliances relating to clinical trials in India.

Recent amendment to Schedule Y of Drugs and Cosmetics Rules, 1945: Recently on 30th January 2013, Government of India came out with certain amendments to Schedule Y of the Rules with a view to tighten the norms relating to the conduct of clinical trials especially in relations to,

1) unethical practice in the informed consent taking process and its documentation. This has led to strict rules being put forth to control such unethical practice. However, considering the diverse socioeconomic and educational status of Indian population, few trial subjects have the curiosity to go through the information given in the "patient information sheet" of the informed consent documents despite detailed discussion with them.

2) Providing the trial subjects or their legal representatives compensation in case of any trial related injury or death. The amendment has enforced complete and ultimate liability on the sponsor of the clinical trial to reimburse any cost incurred by the trial subjects for the medical treatment of non trial related injury (any injury) by the trial subjects as well as financial compensation for such injury or death. Further in case the sponsor fails to provide the proper medical treatment and/ or the financial compensation as per the orders of the licensing authority to the trial subjects (or their representatives), then the authority may cancel or suspend the license of the sponsor to carry out the clinical trials and may even restrict it from carrying any clinical trial in future in India.

3) The amendment also mandates GCP compliance and adverse event reporting.

4) The role and responsibility of the Institutional Ethics Committee (IEC) has been heightened many folds. It is appreciated by all as the IEC functions to safeguard the rights, safety and well-being of trial subjects. In addition, the requirement of the IEC to review and report all serious and unexpected SAE to the licensing authority and the expert committee (in case of SAE leading to death) within 21 calendar days of its occurrence is a very short timeline. In view of the redefined role and responsibilities of the IEC, several full time employed members need to be incorporated to IEC to achieve the goals fixed by the regulatory authority.

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Kolkata

Conclusion: Clinical trials not only contribute to the scientific research and development but also ensure better patient care and in long run is a bonus for the society as it eventually leads to the development of new generic drugs and medicines. Therefore there is a strong requirement for liberalizing the regulatory environment in favour of the people conducting such trials and at the same time balancing the interest of the subjects involved in such trials. The need is to identify and fix the gaps in the regulatory framework and implement existing laws effectively to ensure that clinical trials are conducted with utmost transparency and carefulness. Otherwise we would end up losing the prospects of growth of clinical research activities in India, which could lead to a huge loss to our health care sector.

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Treatment of Palmonary Hypertension and other comorbidities in DPLD

Introduction

Diffuse parenchymal lung diseases (DPLDs) comprise >200 entities and include a wide spectrum of diseases, many uncommon and of unknown etiology, but together accounting for about 1-5% of respiratory practice[1]. DPLDs form a heterogeneous group of lung diseases of varying etiology characterised by the presence of bilateral widespread alveolar shadows in the chest radiograph. The primary diseases qualifying for the terminology DPLD can range from infections through inflammatory and autoimmune disorders to neoplastic conditions. The differential diagnosis and therapy of DPLD can be challenging even to the experienced and astute clinician considering the complexity and variability of etiology as well as presentation. The presence of complications and comorbidities make the therapy even more challenging. It is imperative that the practicing clinician be familiar with the common comorbidities of DPLD and look for their presence which might translate to earlier diagnosis and better subject outcomes. The comorbidities may be nonspecific, which are common to most etiologies of DPLD, or disease specific ones that may be preferential to the primary condition. For descriptive reasons, this short review focuses on the general comorbidities common to most forms of DPLD, with particular highlight on pulmonary hypertension.

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Comorbidities in DPLD

The common comorbidities and therapeutic challenges in DPLD, other than the underlying condition per se, include

1. Pulmonary hypertension, cor-pulmonale and right heart failure
2. Gastro-esophageal reflux disease
3. Osteoporosis and nutritional deficiencies
4. Anxiety and depression
5. End of life issues and need for symptomatic palliation
6. Overlap syndromes with OSA
7. Venous thromboembolic disease
8. Combined pulmonary fibrosis – emphysema syndrome
9. Arthalgia and arthritis

Pulmonary Hypertension in DPLD – Prevalence and Mechanisms

The prevalence and mechanism of pulmonary hypertension (PH) in DPLD varies based on the primary diagnosis, severity of the disease and coexisting conditions. In the lungs, parenchymal and vascular remodeling share common mechanisms that may explain the relatively high prevalence (30–40%) of PH in ILD subjects[2]. The commonest mechanism implicated is the loss of pulmonary parenchyma and alveolar capillary bed with resultant hypoxia and secondary vascular changes including hypoxic vasoconstriction and vascular remodeling in long standing cases. Other mechanisms include disease specific vasculopathy, locally increased vasoreactivity, extrinsic compression of vasculature by lymph nodes, left heart involvement with back pressure extending to pulmonary venous system, coexisting portopulmonary hypertension etc. These mechanisms may be prominent in connective tissue diseases and sarcoidosis[3].

PAH needs to be looked for in each and every case of DPLD and the evaluation should include a targeted history, focused physical evaluation and appropriate investigations. The usual tests required include a 12 lead electrocardiograph, a transthoracic echocardiography with option of right heart catheterization reserved to situation where ECHO findings remain equivocal. Once PAH is diagnosed, the severity needs to be assessed based on the numerical value of PA pressure as well as functional class. A 6 minute walk test provides useful information regarding exercise limitation as well as the need for supplemental oxygen therapy.

Therapy of PH in DPLD

The general measures that need to be adopted in all cases of PH include avoidance of excessive physical exertion, birth control measures in ladies of the child bearing age group, infection prevention with appropriate (pneumococcal and influenza) vaccinations, supervised rehabilitation and psychosocial support. Some other considerations that apply in most cases include the need for anticoagulation, supplemental oxygen in presence of resting or exercise induced hypoxia, addition of diuretics in case of right ventricular failure or volume overload as well as digoxin administration. Advanced therapy targeting PH per se may be an option in a minority of subjects with DPLD. The published evidences in this regard are relatively meager as compared to the volume of research going on in the field of idiopathic pulmonary artery hypertension. The agents available for advanced therapy of PH include endothelin receptor antagonists, phosphidiesterase-5 inhibitors and prostacyclin analogues. Newer agents like soluble guanylate cyclase inhibitors (Riociguat) and antiproliferation agents (Imatinib Mesylate) have been recently launched and await larger clinical experience. Most of the trials evaluating these agents for PH have included subjects with connective tissue disease related PH, although the relative proportion of study subjects with this etiology has been in the range of 20-30% only. The efficacy in the subgroup of patients with CTD related PH have been, in general, inferior to the IPAH subjects although clinically relevant benefits were observed in some studies[4]. Based on the currently available evidences, the primary therapy in DPLD related PH should be directed at the primary disease and should be supplemented by general measures as outlined above. Advanced therapy may be worthwhile in a small proportion of subjects who fail all the aforementioned strategies and may be even used as a bridge to lung transplantation.

PH therapy trials and guidelines in DPLD

The ATS-ERS joint consensus statement on IPF recommends against the routine employment of advanced PH directed therapies in majority of subjects with IPF, but does concede that such an approach may be an option in a minority of carefully selected subjects[5]. This recommendation places a high value on cost and the potential for drug-related morbidity, and a low value on very low-quality data suggesting a possible benefit in selected patients. In an analysis of patients with CTD-PAH including patients with lupus, overlap syndrome and other rheumatologic disorders included in randomized clinical trials of bosentan, there was a trend towards improvement in 6 MWD and improved survival compared with historical cohorts[6]. In systemic sclerosis associated PAH, continuous intravenous epoprostenol improves exercise capacity and hemodynamics compared with conventional therapy although a clear effect on survival in these patients has yet to be demonstrated[7]. In a post hoc subgroup analysis of 84 patients with PAH related to CTD (45% of whom had SSc- PAH), sildenafil at a dose of 20 mg improved exercise capacity, hemodynamic measures, and functional class after 12 weeks of therapy[8]. PH in sarcoidosis has been receiving increasing attention in contemporary literature and a small study published in 2013 revealed improved functional outcomes in 8 subjects treated with vasodilator therapy[9]. The same authors did a meta-analysis of 5 published trials and concluded that targeting PH in sarcoidosis can improve functional as well as hemodynamic parameters. A better survival rate was noted with PH directed therapy in a small group of subjects with pulmonary Langerhans cell histiocytosis although the presence of PH did not appear to worsen the outcome in this small group[10].

GERD in DPLD

Most of the published evidences of GERD in DPLD come from studies on IPF. Raghu et al evaluated 65 subjects with IPF with esophageal manometry as well as pH monitoring and demonstrated abnormal acid GER in 87% of subjects[11]. The disease is asymptomatic in almost half of the subjects and may necessitate invasive evaluation for detection. Standard doses of proton pump inhibitors may not inhibit the acid GER and surgical options may

be needed, but it is unclear as to how much clinical benefit will the abolition of GER provide in IPF. Additionally, the poor lung function precludes an invasive procedure of borderline benefit although there are retrospective reports to the contrary[12]. Recently, the Canadian Scleroderma Research group has demonstrated that presence of symptoms of GERD is associated with progressive worsening of FVC in systemic sclerosis subjects with ILD[13].

Other comorbidities in DPLD

Some of the other comorbidities in DPLD, specifically in IPF, include osteoporosis, nutritional deficiencies, venous thromboembolic disease, lung cancer, overlapping phenotypes with emphysema as well as OSA, respiratory failure, coexisting left heart disease, arthralgia, anxiety, depression and sleep disturbances[14]. Many of them are insufficiently appreciated and inadequately addressed by clinicians, thereby creating therapeutic gaps in DPLD. Osteoporosis can result from primary condition causing bone resorption, steroid therapy, advancing age per se or nutritional deficiencies. Bone mineral density assessment and supplementation as per guidelines for osteopenia is indicated in clinically indicated, if not all, subjects. Smoking can be a risk factor for emphysema as well as IPF and the term "Combined Pulmonary Fibrosis and Emphysema" has been coined to describe this syndrome (better termed as a separate phenotype of IPF) with upper lobe predominant emphysema and lower lobe predominant fibrosis. They might require treatment for COPD as per guidelines. These subjects have poorer prognosis than isolated IPF patients and the outcome is worse if they develop PH. Subjects with obesity and OSA should be treated with positive airway pressure therapy akin to any other OSA subject. Nutrition, psychosocial status and the need for symptomatic palliation should be formally assessed. A comprehensive rehabilitation programme incorporating all these modalities should become part and parcel in the care of DPLD subjects. In advanced disease, discussion of end of life issues and advanced directives should be undertaken.

Summary

DPLDs are associated with many comorbidities which are inadequately appreciated and improperly addressed by the clinician. PH, nutritional deficiencies, arthralgia, symptomatic palliation etc are some of the issues that need to be routinely addressed. A programme of comprehensive care for DPLD subjects incorporating experts from multiple disciplines anchored together by the pulmonologist can provide single step solution to a heterogeneous group of disorders with complex therapeutic challenges. More focused research in this arena to answer many of the uncertainties is a drastic need and should be given top priority.

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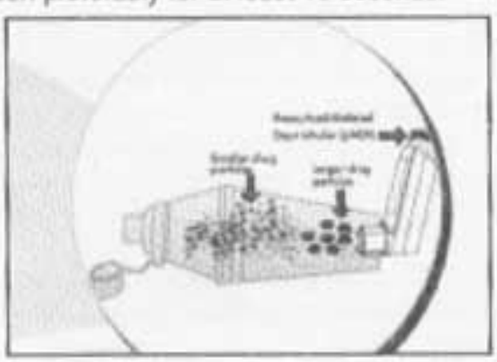
Spacers: Revisting the need in Inhalation Therapy

Spacers are extensions to a pressurized metered dose inhaler (pMDI), with a port at one end to which the pMDI is attached and a mask or mouthpiece fitted at the other end meant for inhalation. They help in holding the medication for a few seconds after it has been released from the pMDI. The pMDI is, incidentally, the most widely used inhaler device in the world, with more than 500 million produced annually.

The working of a spacer: Spacers can be regarded as extension of the mouthpiece of meter dose inhalers. They direct the cloud of medication towards the mouth. When the pMDI is fired or actuated, the aerosol cloud particles produced within the spacer device turns finer and they move slower as they traverse a distance from the release point of the pMDI. The brief stay within the spacer allows the evaporation of the propellants and settling down of the larger particles which in turn increases the amount of drug reaching the lower airways and reduce the deposition of the particles in the mouth and throat. This means less systemic absorption and side effects. About 20% of the dose released from a pMDI gets delivered to the lungs when inhaled through a spacer.

Using a spacer is easy; generally, a patient using pMDIs with a spacer needs to be trained to inhale slowly (30 litres/minute) and to hold his/her breath after aerosol inhalation preferably for at least 10 seconds.



The advantages of a spacer device:

a) Making it easier to use a pMDI - The major problem of co-ordinating the actuation with inhalation of a pMDI is easily overcome by a spacer.

b) Reducing oro-pharyngeal deposition - Due to the speed with which the drug is emitted with a pMDI, close to 70–80% of the drug is deposited in the oro-pharynx. When a spacer is used along with a pMDI, oro-pharyngeal deposition drops by more than 50% since most of the larger particles settle on the walls of the spacer. This reduces the likelihood of local as well as systemic side effects. The British Thoracic Society recommends the use of spacers in patients who are on a high dose of steroids (more than 1,000 mcg/day).

c) Improving pulmonary deposition - The velocity of the aerosol spray is reduced as it passes through the spacer. Also, the propellant droplet size is reduced by evaporation. These result in increased lung deposition.

d) Managing acute attack as an alternative to use of a nebulizer - A systematic review of studies of treatment in children with acute exacerbations of asthma has found a pMDI with a spacer to be as effective as a nebulizer.

Who should use spacers ?

- Children and the elderly.
- Patients with co-ordination problems.
- Those who are prescribed high-dose inhaled steroids (more than 1,000 mcg/day).
- Patients who are prescribed anti-cholinergic drugs (to avoid the spray particles from reaching the eyes).
- Patients with acute asthma requiring high-dose bronchodilators, as a substitute to nebulizers.
- Infants and small children who need inhaled drugs, as spacers can be used with masks.

Types of spacers: As a class, spacers are also known by other names, including "add-on devices" and "extension devices". Spacers can be classified into the following categories:

1. Simple tube extensions
2. Holding chamber:

Simple Tube Spacers - These are open tube spacers with no valve that simply distance the inhaler mouthpiece from the patient's oro-pharynx. Example: Zerostat Spacer.

Holding chamber - Holding chambers share the properties of extension devices, but, in addition, they reduce the need for co-ordination between pMDI actuation and inhalation, and are generally easier for children and older, frailer patients to use than a conventional pMDI alone.

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The holding chambers with valves allow the patient to breathe tidally from the reservoir of drug and are especially helpful for children. The availability of a face mask for use with holding chambers has markedly improved the opportunities for the treatment of very young children with asthma. Example: Zerostat VT.

Factors affecting drug delivery from spacer: A number of factors affect drug delivery through spacers: they are

a) Spacer volume: Optimum is about 250-300 ml

The amount of drug delivered to the airways is inversely related to the volume of a spacer device. The optimum size of a spacer for a young child is approximately 250–300 ml. Very small or large spacers appear to be less effective in delivering anti-asthma drugs. The adults can use both small as well as large-volume spacers. However, the large-volume spacers are bulky and difficult to carry.

b) Spacer shape: Cone, pear or cyclindrical

Spacers are generally of a cone, pear or tube (cylinder) shape. The closer the shape of the spacer to the shape of the aerosol plume discharged from the pMDI, the better it is.

c) Electrostatic charge: Non-static spacer is the best

Among all the factors that influence drug delivery through a spacer, the electrostatic charge has been reported to be the most important. Until recently, all spacers were made of polycarbonate (plastic) material, resulting in accumulation of static charge on the spacer walls. This attracts highly charged aerosol particles from a pMDI, causing their rapid deposition onto the walls of the spacer chamber and rendering them unavailable for inhalation.

A permanent solution to the problem of static charge is to develop a spacer made out of anti-static material like polyamide, e.g. Zerostat VT Spacer. A number of studies, conducted to evaluate the role of static charge on drug delivery have reported significant improvement in lung deposition after removal of the static charge

In an *in vivo* study, the influence of static charge on drug deposition in the lungs was evaluated using a detergent-coated (non-static) and a non-coated plastic spacer (static). Lung deposition of radiolabelled salbutamol was assessed in healthy adults, using imaging techniques. There was a three-fold increase in lung deposition from non-static spacers compared to static spacers (45.6% vs. 11.5%). The mean amount of salbutamol remaining in the static spacers was 76.7% compared to 33.1% in the non-static spacers ($p < 0.001$).

Some facts about the spacer use:

a) pMDI + Spacer : as effective as a nebulizer:

Several clinical studies have shown that spacers are at least as effective as nebulizers in the treatment of severe acute asthma attacks. However, the advantages of spacers over nebulizers include improved delivery efficiency, greater convenience, low risk of pulmonary infection, greater speed of administration and cost-effectiveness

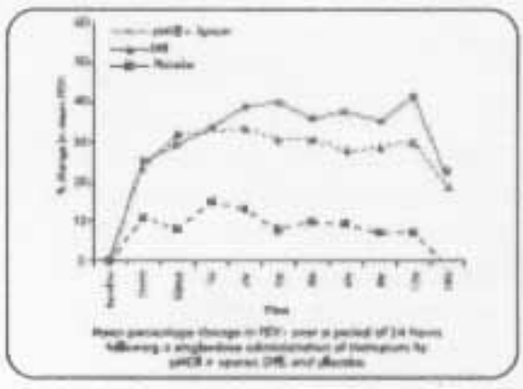
Several clinical studies have shown that spacers are at least as effective as nebulizers in the treatment of severe acute asthma attacks. However, the advantages of spacers over nebulizers include improved delivery efficiency, greater convenience, low risk of pulmonary infection, greater speed of administration and cost-effectiveness

b) pMDI + Spacer : as effective as a dry powder inhaler:

A randomized, double-blind, double-dummy, three period, placebo-controlled, crossover, single-centre study was conducted in 19 patients with stable chronic obstructive pulmonary disease (COPD).

Tiotropium, administered through both a pMDI (with spacer) and a DPI, showed significantly better mean FEV_1 ($p < 0.01$) and mean FVC ($p < 0.01$) differences from baseline, as compared to placebo. There was no difference in the efficacy between the pMDI and the DPI.

Thus, tiotropium administered through a pMDI and spacer can be used by those COPD patients who prefer to use the pMDI device, and especially in those who cannot generate sufficient inspiratory flows required for using DPIs.



c) pMDI + Spacer : as effective as a breath actuated device

In a randomized, double-blind, crossover, placebo-controlled study, 18 subjects with stable, moderate, asymptomatic asthma were subjected to a methacholine challenge test.

Administration of salbutamol via a pMDI + spacer or by the Autohaler, a breath-actuated device, resulted in a similar bronchoprotective effect against methacholine, as seen by the increase in PD20.

Inference: It is important to appreciate the role of this small device in aerosol therapy. A spacer and a SOS inhaler (salbutamol) can act as the best friend at emergency situations and can serve the purpose of a nebulizer. One need to use three to four puffs every 10 - 15 minutes for a few times (three or four) to get the effect of a nebulization. Using a spacer with valve should always be preferred.

Reference: 1) Clin Pharmacokinet 2004; 43 (6): 349 – 60. 2) Lancet 2011; 377: 1032 – 45. 3) S. A. Respir J 1998; 4: 25 – 29. 4) Pulm Pharmacol & Ther 2001; 14: 351 – 366. 5) Eur Respir J 1999; 13: 673 – 8. 6) Respir Med 2007; 101: 2464-2471. 7) Chest 2000; 117: 1319-1323

NEW HORIZON :-

The universe of stem cells and mankind.

All of us are born from a single cell resulting out of fusion of a particular sperm and particular ovum of our parents. The universe of our body is created out of that "fused" cell with chromosomal content of 23 pairs; 50% of which being contributed by each our parents.

That initial cell was the main progenitor cell for all cells lines we possess and that very cell with its next series of mitosis vertically lead to development of progenitor cell lines for deferent organogenesis. They are also stem cells. They do not just evade with our birth; they stay in different forms to guide our development and repair and to modulate the activities and survival of the different tissues till our last breath. They help repairing injury and they cause relapse of diseases. Hence, in every physiological / pathological activity they remain silent but to lead us through the complexity of self-environment interaction throughout our life.

Only recently we have started understanding them and despite the huge claims and bulk of papers, the understanding is really miniscule compared to the vastness of their existence and function. We have possibly just entered a new universe and our journey into it can bring us life and happiness in future along with new challenges and threats.

Stems cells: Stems cells are undifferentiated precursor cells. They possess the capacity to differentiate into different cell lines and can renew themselves. They may be pleuripotent (can differentiated into 'n' number of cells of lineages) or multi potent (multiple lineages)

They are basically classified as

a) HSC: Hematopoietic Stem Cells
b) MSC: Mesenclymal Stem Cells
c) EPC: Endothelial progenitor Stem Cells
d) Organ Specific Stem Cells

The stem cells can be "embryonic" or 'adult': the adult stem cells remain in the body throughout the life while the "embryonic" cells gradually evade from the system.

Isolation and identification of different type of stem cell is difficult and still needs a better clarification. The use of stems cells as a source of tissue / organ regeneration needs a lot of research. Though in animal model and in limited human experiments with different diseases, stems cells have shown promising results, there are many issues lying unresolved relating to choosing the right kind of stems cells or combinations, the dose, the route of administration and others

The universe of stem cell related science is like a magnanimous sea where the human breed has just touched its shore. There are possible profuse wealth and unknown threats in future of stem cell use. We shall have to wait for some time to see further development till it settles down to defined clinical recommendation for different diseases. We may hope to find some answer for acute lung injury, IPF and COPD like diseases in future with the use of stem cells.

Cancer stem cells: It is always unfortunate to see a cancer to recur after being treated well with demonstration of regression and even subsequent stabilization.

Scientists believe that this happens from the cancer stem cells (CSC). These cells are phenotypically distinct cells with tumorogenic potential. Many such cancer stem cells

have been demonstrated in different hematological malignancies and also in different solid tissue tumor.

The CSC hypothesis conceptualizes that like all other organs any cancer too has its progenitor cells committed to differentiate into cancer and preserve its property of self renewal for relapse and also drug resistance which is found as in some malignancies.

Isolation of different CSC and their phenotypical characterization has been largely possible with the use of the presence of different cell-surface makers as CD133, CD44, etc. and the aldehyde dehydrogenase (ALDH) activities.

It is also postulated that normal stems cell activities suppress the manifestation of the CSC activity. Dysregulation of normal SC activities may be involved to drive activation of CSC in making different tumors.

Several agents are now in the process of development to target the cancer stem cells as well. It will be interesting to see how these new agents change the prospect of relapse free survival of different cancers including bronchogenic carcinoma.

JOURNAL CLUB

Mycobacterium tuberculosis septic shock.

Clinicians often fail to consider sepsis and septic shock from mycobacterial tuberculosis. Though uncommon, it remains a well recognized syndrome.

Recently a retrospective nested cohort study looked into the clinical characteristics, epidemiological risk factors and covariates of survival in patients with MTB septic shock compared to other bacterial shocks. The following remains the fact sheet for M. tuberculosis septic shock

- FIt constituted <1% of total patients of septic shock
- The in-hospital mortality rate is high (79.2%) compared to the septic shock from other bacterial infection (49.7%)
- Near 90% of MTB septic shock had respiratory tract involvement.
- Over 55% of them have disseminated infection.
- Inappropriate and appropriate empirical therapy resulted in survival rate of 7.1% and 36% respectively and those not treated all died.
- Early treated patients had better survival prospect.

The study inferred that tubercular (M tuberculosis) septic shock behaves similar to bacterial septic shock and one needs to be aggressive to recognize and treat it.

Chest 2013:144(2), 474 – 482.

Breath analysis to diagnose OSA:

Traditionally the diagnosis of OSA demands a sleep study which is cost and time intensive. Recently a research looked into the prospect of identifying OSAs by electronic nose.

In a cohort of 40 OSAS and 20 healthy controls they identified a linear discriminating function separator between OSAS from control ($P<0.005$) suggesting that electronic nose can distinguish OSA syndrome patients from controls with high accuracies

ERJ. 2013: 42(1), 145-155

Transfusion of mesenchymal stem cells in COPD.

Stem cell therapy has been regarded as the "horizon of hope" for several diseases including COPD – a chronic progressive inflammatory airway disease.

A study was conducted to look further into the safely and potential efficacy of systemic stem cell administration in moderate COPD patients in a double blind fashion. The patients received four monthly infusions of stem cells and were subsequently followed for 2 years.

62 patients were recruited in different centers. There was no improvement in the stem cell receiving group in terms of lung function, quality of life, 6 minute walk distance, but as regards inflammation there was a significant early drop in the CRP level in the treated group of patients. There was no untoward reaction with mesenchymal stem cell therapy.

Chest: 143(6), 1590 - 1998

Circadian rhythm in ICU patients: the sicker are more prone to suffer.

ICU patients stay in an artificial environment in stress and often being disconnected to exposure to sun or even site of outside nature. Hence, the disturbance in circadian rhythm is natural.

A recent study looked into the issue and revealed a significant predictive power of the severity of illness (in terms of APACHE III score) to correlate significantly with the circadian displacement.

Chest 2003; 144(2), 483-489.

TANTU

Tantu is our friend. He always teaches us.

Conversation on diagnosis of PH: a case based approched

My good friend was a little excited today. He just finished a round with the second year PG students and hurried to the doctors' room. This appeared unusual to me and when I began to guess the reason quietly, Tantu himself broke the silence.

Tantu: "can you leave a poor patient untreated just to satisfy a guideline recommendation"?

I know that the question is directed to me and I wish a dialogue to break in. But I slowly looked up at Tantu and asked "why are you blaming guideline? I cannot follow you, please elaborate".

The reply was immediate:"would you treat a case of corpulmonale with overt right heart failure?"

"Yes, if I feel so: which guideline bars you from doing that?" I questioned back.

Tantu opened himself;"see, today in the morning round your most favorite student asked me to justify my decision."

I know whomTantu is referring to. Shyamal is a bright young PGT whom I like for his sincerity and frankness. He frequently bothers us with questions beyond text book writings.

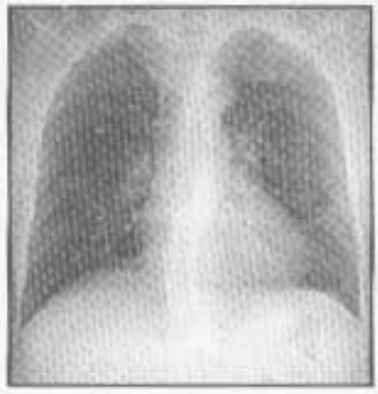
I replied – "that's good, we must encourage them to ask and question us, or how come they be good teachers as one like you in later life."

Tantu: "Oh! I didn't mean that. Do you think practice of medicine is all scripted in guidelines and you have no room to decide treatment on individual merit?"Tantu continued: "does a guideline made at USA fits your soil as aptly as it fits in America?"

"Surely not;" I answered, "but will you please tell me what went wrong with Shyamal?"

Tantu: "We were at the bedside discussion of an advanced COPD patient with corpulmonale. He has been on diuretic and oxygen and all other possible therapy for COPD without any significant co-morbidity and we were discussing his X-ray.He had raised neck venous pulse and had P_2."

Tantu took out the X-ray plate from beneath the news paper. I know that he has brought the film to engage me in the discussion. It was a classical x-ray of any COPD patient but with non tubular heart, slight bulging of the Rt. border and prominent pulmonary arteries.

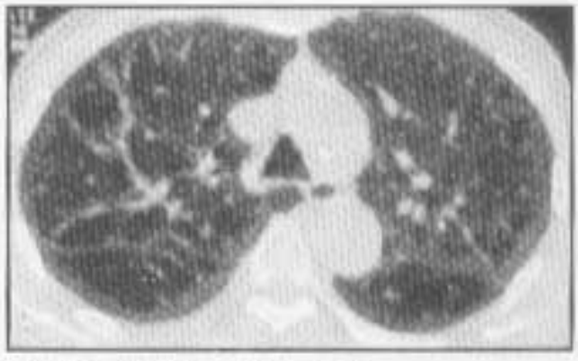


I looked the x-ray and said, "what is very special in it – the whole thing suggests COPD with likely PH (pulmonary hypertension)"

"Good!"Tantu said – "now look at the HRCTplate."

I know Tantu is fond of asking HRCT chest often for COPD patients and he discussed the reasons once with me. I accepted his arguments justifying the utility.

I made a glance at both the mediastinal and lung window cuts against the view box now. Yes, clearly emphysemawith pulmonary trunk being overtly dilated and visually the diameter exceeds the aortic root diameter. The pulmonary artery branches too were diluted all the lobes.



"What do you think?" Tantu asked

"This poor guy has PH and the PA pressure is likely quite

high. I went on saying – the patient must be quite symptomatic with dyspnoea and may be having resting hypoxemia and desaturation even with slight exercise."

Tantu looked happy: "Yes, you are right. This guy has COPD and severe shortness of breath; his FEV1 is incidentally 65% of predicted."

I know Tantu is dragging me to say more. So I continued further: "for pure COPD such degree of PH is found in only those patients have mild to moderate COPD patients. But, the disease looks quite advanced. So, we may have to exclude other causes of PH in him. I think that his DLCO would be around 25 -30 % and if we fail to find any other cause contributing to PH, the story may deserve to be reported."

"By the by", I asked,"what is his BMI"; and continued "from the soft tissue thickness it looks that the gentleman is quite hefty. I will seriously suspect OSA even from this HRCT'. Further looking at the heart I murmured (enough to make it audible to Tantu) 'this guy has probably LVH and left ventricular hypertrophy and may even can have ischemic heart disease. I seriously do not buy the theory of no co-morbidity'. He has likely left ventricular diastolic dysfunction"

Tantu: "Great! This why I like you and this is why I have carried the plates to the doctors' room. The gentleman has gained 7 Kg of body weight in last one year and; his present BMI is now above 30 and he has hypertension detected for two years. Overtly, he is sleepy all the time and the other patients were unhappy for his loud snoring".

"But where is the problem?" I asked Tantu.

Tantu – "the problem is at the mindset". Tantu made a pause and continued: "when I recommended sildenafil to his prescription along with auto CPAP your 'good' student said that I cannot do so as it is going against the guideline recommendations. Do you think thispoorpatient need to undergo right heart catheterization (RHC) to establish PH before initiating treatment? Look, his resting oxygen is barely 88 % even when he is awake"

Now I could get the scene clear and understand why my friend is excited. I know his mind.

'Tantu, those guidelines are no laws or the constitution of India; they are just recommendations for streamlining practice for common situations to offer evidence based therapy with avoidance of errors'.

Tantu: 'fine but stop this bookish talk. They could be like the "Bible" for those who base their practice on so called evidence and not on conscience. And that's how they create more problem for themselves and the patients too. May I ask you a small question?'

"Why not ?" I said

Tantu: "Can't you diagnose PH without right heart catheterization?"

"Yes, why not – like in this patient, it is very obvious. The widening of the right pulmonary artery in Chest x-ray (PA view), the signs in HRCT are enough and specific for the presence of PH. By the by, I asked, what is the Doppler echo report."

Tantu, "concentric LVH, LVDD grade II, with PA pressure (syst) as 65 mm."

"Then where is the problem to start anti PH therapy?" I asked.

Tantu: "That is what I said, but the students quoted the guidelines and showed smartness saying neither European nor American guidelines recommended treatment without RHC. It seems that we are slaves of America and Europe". Tantu looked excited again.

"Relax my dear: they are students and it is good that they read guidelines seriously. People like you make guidelines and guidelines can also be changed. No sensible person will agree that guideline is the Bible or Gita."

It worked, Tantu looked a little relaxed

Tantu: "I can't stand people being deprived altogether from the benefit of treatment for overt PH just because right heart catheterization is not possible or not done. I will never ever recommend RHC to a patient who finds it difficult to purchase his daily medicine for sake of confirmation when I am convinced to my mind that he or she has PH to cause his symptoms from the other available investigation".

I remained quiet.

Tantu continued: "Don't you think those observations is CxR (PA) and HRCT chest are evidences and don't you think that it they are further supported by echo (may not that specific for diagnosis according to be your books) is enough to stamp PH. And then, for a patent, what is the harm to extend the benefits PH specific therapy even

if I do not know the exact PA pressure"-especially when the underlying disease is taken care of?"

I got impressed again with my friends love and commitment for his patients. I know him for a long time – he never bothers for money or fame – and I watch himturning joyous like a child to see relief of symptom in his patents.

"Tantu, you are correct, I second you whole heartedly. I know that physicians like me in the developing world will support your view." I supported him in an emphatic tone.

Tantu: "Then why not make our own guideline?"

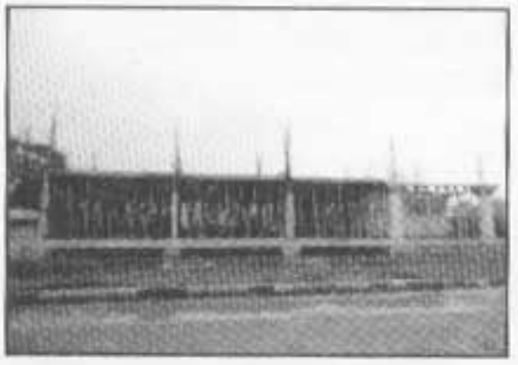
"It is good idea, lets test your organizational capacity again," I said.

"Welcome!"

Tantu looked happy – I stood up to move for the radiology round and told him– "please do not be annoyed with your students; rather instill this spirit of love and judicious decision making power in them – this world needs people like you."

NEWS FROM THE INSTITUTE

The construction of our new campus is ongoing based on donation been available.



In the scientific front we are engaged in a few interesting research projects.

We had 3 publications in last one year and four of manuscripts are there under review in different international journals.

The Rural COPD programme is ongoing – we have found the curriculum based single point semi supervised education and training programme to be effective (statistically significant) in our rural COPD patients. (manuscript ID. COPD-2013-0165 COPD journal)

So far we have screen over 7000 population in 8 villages of Rajnagar and Mayureswar block and have diagnosed 200 COPD patients according to the GOLD guideline using spirometry.

The prevalence of COPD in symptomatic adult (>40yrs.) population stands as 8.99% (see abstracts fro Pulmocon '13)

The Pulmocon 2013 has been scheduled for 28th and 29th of September with the central theme as "Lungs in systemic diseases". The 4th Acharya Prafulla Chandra Roy Award is going to offered to Prof. Ajoy Kr. Roy and the 5th Dr. S N De memorial oration will be delivered by Prof. Dr. M. S. Valiathan.

The Institute is as active as before in its education, welfare and benevolence efforts.

ABSTRACTS FOR PULMOCON -'13 : Received Before 20-9-13

Title: Formation of an assessment tool to measure the Quality of Life (QoL) of patients of DPLD (diffuse parenchymal Lung diseases) on a newly develop questionnaire.

Authors: *Dipanjan Saha , Soumen Kumar Das, Protyaya Deep Bhattacherjee, Ratna Dey, Malabika Ghosh, Madan Sarma, Rana Dey, and Parthasarathi Bhattacharyya, Institute of Pulmocare and Research , Kolkata*

Background: The measurement of the QoL (Quality of life) is important to understand the status, behavior, and the effects of interventions for a particular disease. Incidentally there has been no good QoL assessment tool for the DPLD patients.

Objective: to try to make a questionnaire based instrument to enable a physician note the QoL of DPLD patients in day to day practice

Methods: A 18 point questionnaire has been formed on 10 patients' perceived domains based on the existing knowledge to assess the QoL of DPLD patients in a consensus through series of group meetings among the members of a dedicated team of doctors treating DPLD. The instrument was tested on 10 DPLD patients randomly and modified accordingly without any change / addition of domains. The instrument thus formed was named as PILD (Pulmocare Interstitial Lung Disease) questionnaire and was applied along with other parameters of QoL assessment as SGRQ, Borg's scale, visual analogue

scale CAT (COPD Assessment Test) score and also with lung function test to a cohort of DPLD patients. The response collected through the application of the new instrument were correlated to the result available through use of the other known instruments.

Results: 89 patients (51 males and 38 females; mean age 57.88±10.43 years) responded. The PILD score has shown to have significant ($p<0.01$) positive correlation FVC pre absolute and percentage value, SGRQ total score, , VAS and the CAT score and 0.0296 with Borg's scale,and the correlation co-efficient being 0.13, 0.09,0.78, 0.8,0.8, and 0.65, respectively.

Inference: The newly developed QoL questionnaire with 18 questions covering on several domains of the life of DPLD patients has been found to correlate well with the other existing and widely used QoL assessment instruments. But it needs further validation.

Title: Pancreatic pseudocyst with cysto-pleural fistula managed by endoscopic stenting

Authors: *Dr Mohamed Shafiq U, Dr Asmita Mehta, Dr Rajesh V, Dr VP Gopinathan*

Affiliation: Department of Pulmonary Medicine, Amrita Institute of Medical Sciences and Research Centre, Ponekkara, Kochi-41, Kerala. PIN 682041

Background: Pleuropulmonary manifestations are common in pancreatic disease, both acute and chronic. The mechanism of pleural effusions in chronic pancreatitis is pseudocyst formation and pancreaticopleural communication. Distal pancreatic communications with pleural space are usually not amenable to endoscopic techniques and often necessitate surgical correction. We report the case of a young gentleman with previously unsuspected pancreatic pseudocyst and recurrent pleural effusion due to distal pancreatico-pleural communication who was successfully managed by endoscopic stenting.

Methods: A 36 year old gentleman was referred with a suspicion of MDR tuberculous pleural effusion. He was a chronic consumer of ethanol. A presumptive diagnosis of tuberculous pleural effusion had been made 2 months back in a primary care setting based on exudative lymphocyte rich pleural fluid. There was reaccumulation of pleural fluid despite regular therapy with anti tuberculous drugs.

Results: Pleural fluid cytology was negative for malignant cells and ADA levels were low. Amylase levels in the pleural fluid were significantly high. CT abdomen revealed features of chronic calcific pancreatitis with a pseudocyst near the tail of pancreas. ERCP revealed contrast leak into the left pleural space through a well formed track between the pseudocyst and pleural space. By-passing the pancreatic end of the fistulous track with an extraordinarily long stent led to resolution of pleural effusion.

Conclusions: Pancreatic pseudocyst with fistulous pleural communication should be considered in the differentials of recurrent undiagnosed pleural effusion. Although many cases need surgical assistance, the present case was managed successfully with endoscopic stenting.

Corresponding author: *Dr Mohamed Shafiq U; Email : drshafi_1976@rediffmail.com mobile : 08943814985*

Title: Indications and Implementation of Pneumococcal Vaccination in Pulmonary OPD practice

Authors: *Dr Amit Gupta, Dr Asmita Mehta, Dr Rajesh V, Dr VP Gopinathan*

Background: Invasive pneumococcal disease is the commonest vaccine preventable cause of morbidity and mortality across the globe. The United States Advisory Committee on Immunisation Practices has laid down indications for pneumococcal vaccination in adult clinical practice. Despite this, the physician awareness and implementation remains suboptimal. The present study attempts to unravel the indications of pneumococcal vaccination in adult subjects attending pulmonary medicine OPD of a tertiary care institution and adherence to the recommendations.

Methods: This was a cross sectional study. Subjects attending the pulmonary medicine OPD for a month were evaluated with history, examination and relevant investigations as to the need for pneumococcal vaccination. The indications were noted down. The proportion of subjects who actually underwent vaccination was recorded and the reason for non adherence was noted.

Results: 651 OPD patients were evaluated. Among them, 423 (65%) subjects had indications for pneumococcal vaccination, of which 177 were already vaccinated. Among the remaining 246, only 74 (30.1%) actually received the dose. The common reasons for non implementation included omission by doctor (37 subjects; 21.5%), procrastination by subject (54 subjects; 31.4%), denial due to economic reasons (20 subjects; 11.6%), concerns of safety (11 subjects; 6.4%), needle phobia (9 subjects; 5.2%).

Conclusions: A vast majority of subjects had one or more indications for pneumococcal vaccination. Physician implementation and candidate acceptance of the strategy remains sub-optimal. There is a compelling need for instituting an institution approved vaccination protocol.

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Title: History of Pulmonary Tuberculosis and Pulmonary Hypertension: coincidence or association?

Authors: *Dipanjan Saha, Pratyaya Deep Bhattacherjee, Soumen Kumar Das, Ratna Dey, Malobika Ghosh, Iti Dutta, Madan Sarma, Arko Ghosh, Parthasarathi Bhattacharyya. E-mail : parthachest@yahoo.com*

Background: Pulmonary tuberculosis is not listed as a cause of PH.

Method: In a prospective study we looked for the presence of history of pulmonary tuberculosis in our attendees at IPCR outdoor amongst those who were diagnosed to have pulmonary hypertension from varied etiologies.

Results: A total 194 out of 2347 patients were detected to have PH; of them 25 (12.76%) patients had PH associated history of treatment of tuberculosis. When these patients were further analyzed on the spirometry results, those with history of smoking (n = 14) behaved as COPD (FEV1/FVC as 56.55) with %FEV1 40.23 (± 15.62) and absolute value 1.01 ± 0.31 while those without history of smoking behaved like ILD with FEV1/FVC of 79.33 (± 19.93) and % FVC as 49.67 (±11.54). The first group with history of smoking shows features of small airway obstruction (%FEF_{25-75} 17.65 ± 8.34) and the other (without history of smoking) had none such change (FEF_{25-75} = 63.83 ± 48.61). The PA pressure (mm of Hg) was however higher in non-smoker group (46.25 ± 7.42) than the smoker (44.08 ± 8.86).

Inference: Pulmonary tuberculosis is likely to produce PH independent of the history of smoking. The observation needs further investigations.

Title: Neural network model for Asthma characterization

Authors: *Dev Kumar Das, Parthasarathi Bhattacharya, Chandan Chakraborty*

School of Medical Science and Technology, IIT Kharagpur

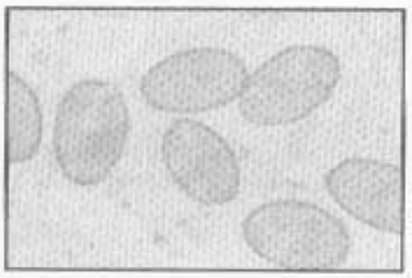
Prevalence of asthma is difficult to determine as there is an overlap with other respiratory conditions, such as chronic obstruction pulmonary disease. This has caused a substantial increase in the cost of providing therapeutic interventions and health care facilities for such patients. As such, combinational approach using clinical diagnosis and spirometric information of affected patient along with its follow-up on regular basis becomes very important. In view of this, the objective of the present study was to develop pattern classification methodology for automated detection of asthma using artificial neural networks. Here, we have employed two types of neural network viz., probabilistic and radial basis function [RBF] for characterizing clinical and spirometric data towards asthma diagnosis. Both clinical and spirometric information have been analyzed wherein, the set of statistically significant features were separately fed to the two neural network models and their performances evaluated. It was observed that both probabilistic and RBF neural network provided similar performances towards asthma classification with overall accuracies 92.59% and 92.69 % respectively.

Title: Paragonimus Lung Infection Case report.

Authors: *Dr. H. Sunanda Devi, Dr. Chultin Lepcha,*
Department of Respiratory Medicine
RIMS, Imphal.

Abstract: Human infection by the lung fluke *Paragonimus westermani* is widely distributed in Africa, Asia, and South America. Transmission of the parasite to humans primarily occur through the consumption of

raw or undercooked crabs. The cercariae ingested orally transit the intestinal wall and migrate through the peritoneal cavity across the diaphragm into the pleural cavities and then into the lungs, where they ultimately lodge. They may survive upto 10 years in the body. We report a 17 year old patient who came with difficulty in breathing, chest pain and cough with haemoptysis with a history of crab intake since 7 yrs and above. On chest x-ray there was right upper zone consolidation and paragonimus egg was detected on sputum microscopy. The patient responded to praziquantel therap.



Egg of Paragonimus westermani found in wet mount sputum.

Title: COPD in symptomatic adult population in rural West Bengal: a spirometry based prevalence analysis.

Authors: *Madan Sarma***, Dipanjan Saha##, Bodhiswatta Chakraborty##, Rana Dey##, Ratna De##, Partha Bhattacharjee##,Pallav Bhattacharyya##, Soumen Das##, Saswata Ghosh#, Moloy Bhattacharya****, Ratan Lal Manna****, MD. Nizamuddin****, Dharam Sutradhar****, Sanjoy Mondal****, Akal Mal****, Pintu Bagdi****, Avijit Chowdhury**, Saibal Mukherjee**, Nemai Mishra##, Rupak Ghosh*, Parthasarathi Bhattacharyya*.*

Objective: to look for the prevalence of COPD in rural Bengal in adult male and female population with respiratory symptoms above 40 years

Methods: eight villages of the Rajnagar and Mayureswar block of Birbhum district (West Bengal) were chosen for an epidemiological survey for presence of COPD in adult symptomatic population. From a population registry been made through a door to door systematic survey of those villages, the population above 40 years were screened with a questionnaire for presence of respiratory symptoms (cough, wheeze, expectoration, shortness of breath, and hemoptysis) and those having a positive response (one or more of the above) were screened with spirometry observing the ATS guideline. Out of them, those showing obstructive changes according to the GOLD criteria (with post bronchodilator FEV/FVC < 70%) were included for analysis as COPD.

Results: out of a total population of 7004, 2224 were adults above 40 years. Out of them 1099 (49.41 %) of people had one or more respiratory symptoms and 200 subjects from them turned out to be suffering from COPD making the prevalence as 8.99 % in the selected symptomatic population.

Inference: spirometry based COPD prevalence in symptomatic adult population has been found to be much higher than the estimated national average of COPD prevalence. It suggests that defining the dimension of the problem demands the use of objective method as spirometry. The actual COPD load in the country could be far higher than estimated.

Consultant Institute of Pulmocare and Research, *West Bengal Liver Foundation, # Institute of Developmental Studies, Kolkata, * Field coordinator, ## Research workers, ****Volunteers*

Title: Detection of Cardiac Status Using A Robust Wavelet Based Technique

Authors: *Ashok Mondal*, P. S. Bhattacharya†, Goutam Saha§*

Background: Medical practitioners listen to heart sounds using a stethoscope device and make interpretation regarding the diseases if any. Its performance depends on the physicians experience and knowledge. There is a probability of misinterpretation due to human factor involved and presence of different interfering signals. The objective of our work is to develop a robust automated tool that can diagnose cardiac status in noisy clinical environment.

Methods: The recorded heart sound signals are contaminated with noises produced from different sources namely environment, data recording and processing instruments and man made disturbances. These noise sources lead a misinterpretation of the cardiac status. In this study, the instrumental hazards and man made artifacts are reduced by using a first order differentiation algorithm [1], and properly placing the stethoscope on the body surface of the subjects. The surrounding noise are removed by Singular Spectrum Analysis (SSA) based method [2]. The analysis of enhanced heart sound sig-

nal is performed in two stages: wavelet domain feature extraction [3] and binary decision regarding the cardiac status [4]. The block diagram of the proposed technique is shown as a flowchart in Fig. 1.

Results: The performance of the proposed method is evaluated through statistical analysis and given in Table 1. The proposed method gives an accuracy of 100% for a database of normal and 8 pathological classes. The derived algorithm is very fast, it takes about 3 Sec to execute a cycle.

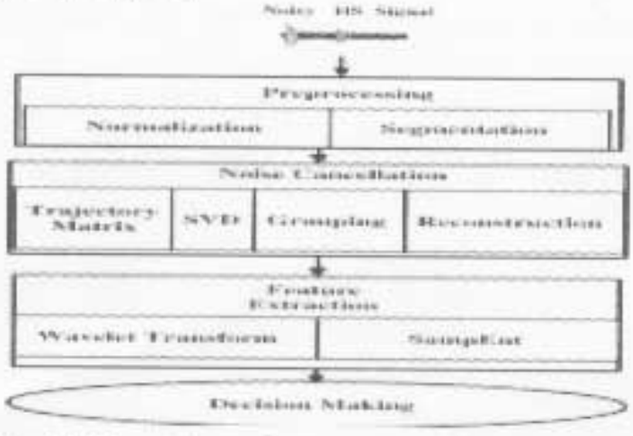


Fig. 1. Different stages for assessing of the cardiac status

TABLE I

ASSESSMENT OF CARDIAC STATUS USING SAMPLE ENTROPY PARAMETER FOR NORMAL AND ABNORMAL INDIVIDUALS

Pathology	NR	SEV($\mu \pm \sigma$)	DC
Normal	25	0.7734±0.0873	Normal
Aortic Insufficiency	22	1.1372±00.0445	Abnormal
Aortic Stenosis	28	1.6732±0.0472	Abnormal
Atrial Septal Defect	25	1.7222±0.1283	Abnormal
Early Systolic Murmur	25	1.0950±0.0585	Abnormal
Late Systolic Murmur	28	1.2095±0.0411	Abnormal
Mitral Regurgitation	32	1.6400±0.2951	Abnormal
Pan Systolic Murmur	25	1.4173±0.0377	Abnormal
Pulmonary Stenosis	28	1.5103±0.0527	Abnormal

NR: Number of Recordings; SEV: Sample Entropy Value; i: Mean; : Standard Deviation; DC: Diagnosed Condition.

Conclusion: The derived algorithm can be used as a diagnostic tool that will assist the physicians in prognosis the cardiac status: normal vs abnormal in a noisy clinical environment.

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Title: Effect of Doxycycline on Factors Associated with the Pathogenesis of Chronic Obstructive Pulmonary Disease (COPD)

Authors: *Brajesh Singh[1], Elavarasan Subramani[2], Parthasarathi Bhattacharyya[2] and Koel Chaudhury[1]*

Background: Endothelial nitric oxide synthase (eNOS) is associated with adhesion, extracellular matrix (ECM) degradation and inflammation in COPD. Adrenomedullin, a potent vasodilator, promotes angiogenesis mediated by the eNOS signaling pathway. Increased levels of E-selectin in COPD indicate that the patients are susceptible to exacerbation. Doxycycline (Dox), a safe antibiotic with documented long-term dose, is known for its ability to inhibit matrix metalloproteinases (MMP), enzymes actively involved in ECM degradation. Since recent studies suggest altered adhesion signaling pathways, extracellular matrix (ECM) degradation and inflammation to be the key underlying mechanisms in COPD, the present study aims to investigate the effect of Dox on MMP-2, eNOS, adrenomedullin and E-selectin in COPD cases.

Methods: 20 patients diagnosed with COPD reporting at the Institute of Pulmocare and Research Centre (IPRC), Kolkata, India were included. The research was approved by the IRB. The effect of Dox (100 mg twice a day for 3 months) was assessed pre- and post-treatment

and compared. Expression level of eNOS, MMP-2, adrenomedulin, and E-Selectin were measured in serum twice, once during the first visit and second after 3 months of Dox treatment. Written informed consent was obtained from all participants.

Results: A significant decrease in eNOS ($P<0.001$), adrenomedulin ($P<0.005$), E-Selectin ($P<0.005$) and MMP-2 ($P<0.005$) was observed in the post-treatment group as compared with the pre-treatment cases.

Conclusion: Long-term use of Dox in COPD appears to decrease the angiogenenic, inflammatory, matrix degradation and cell adhesion markers to a considerable extent. This study warrants further validation with additional markers assessment in a large sample size. Future research on Dox-induced alterations in the eNOS pathway in COPD patients is proposed.

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About the Institute

The Institute of Pulmocare & Research was born in 2000 AD with a motto of Research, Education and Patient care.

With increasing urbanization, pollution, and other factors, the respiratory problems are on a rise. The institute is devoted to address them in an organised fashion, with research activities to the best of its capacity.

Thus, to its credit, the institute has already been granted the recognition as a Scientific and Industrial Research Organization by the Government of India. In the Institute, we have innovated some novel treatment approaches for different lung conditions and our activities have attracted attention and appreciations from all concerned. We are also involved in benevolence with significant rural activities.

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