University of Medicine and Pharmacy “Gr.T.Popa” Iași

General Medicine Faculty

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DOCTORAL THESIS

Peripheral arterial disease and chronic obstructive pulmonary disease in smokers

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IASI - 2014
Introduction

The present work is justified by the absence of clear data regarding the mutual relation between the Peripheral Arterial Disease (PAD) and the Chronic Obstructive Pulmonary Disease (COPD) at the smoking patient, considering the fact that smoking is a major risk factor in both afflictions. Dangestel(1) and Galal (2) attempt to address this theme.

The fact that all major specialty works place smoking in the first place in the ethology of both diseases (3,4) makes the absence of significant approaches of these aspects hard to understand. Even if in the last few years some publications took into consideration the PAD-COPD interrelation, from a therapeutic and prognostic point of view, we can only talk about a beginning in the exploration of this theme.

Neglected for a long time, PAD begins to be rediscovered pathologically, due to both its increasing frequency and its positive correlation with the rest of cardiovascular comorbidities. Bhatt(3) proves that over 60% of patients suffering from PAD also have multivascular disease (coronary and/or cerebrovascular). Also the risks of stroke, myocardial infarction and cardiovascular related death are 2-3 times, 4 times and, respectively, 6 times higher in these patients. These explain the raising interest in the diagnosis and treatment
of PAD. A significant example that proves this is offered by one of the most important modern cardiology handbooks: “Braunwald’s Heart Disease-A Textbook of Cardiovascular Medicine“. In its 5th edition (1997) (19) the handbook did not even present PAD as a subchapter, while beginning with the 7th edition (2005), it devotes a distinct, more consistent chapter to peripheral arterial diseases.

This sudden raise in interest may be partly explained by the fact that PAD is one of the most “tangible” and disturbing ways in which tissue ischemia manifests itself. Beyond pain, PAD’s damage can be seen, and being seen, it is understood; the patients with a severe form of arterial disease see and understand that a segment of their own body is being destroyed, while those with incipient forms can observe the ones who are more severely afflicted. In contrast, myocardial infarction (a result of coronary ischemia) hurts, kills, but is not seen; stroke (a result of cerebral vessels ischemia) causes paralysis/paresis, aphasia, ataxia, major handicap and death but again, it does not have the same visual impact! Moreover, recent epidemiological data show a prevalence between 4.3% and 29% in ample studies conducted in North America and Europe (4,5). The indubitable major risk factor is smoking, a fact that is also proven by the author of the PhD thesis, presented at various national and international
manifestations and published in specialty editorials (21, 22, 35); besides, it is this direct personal experience gained over a period of more than 12 years of clinical approach of PAD, obtained by direct investigation (including operational invasive), treatment and supervision of over 1200 patients, that offered us the support and motivation for elaborating this PhD thesis (this experience entitles us to at least hope that we can prove the necessity of further research on the topic of PAD-COPD interrelation).

Other major risk factors in the development of PAD are: diabetes mellitus, arterial hypertension, hypercholesterolemia, age of more than 65.

The association between COPD and smoking has been known for over 50 years; even if the ethology of the disease is multifactorial, smoking is the most important risk factor (80% of COPD’s ethology) (6). There is also a clear dose-effect relationship between smoking and the risk of developing COPD and its severity.

Both the negative prognostic influence of continuing smoking, after diagnosis and beginning of treatment in both diseases and the benefits of quitting smoking in the same conditions have been strongly established (7, 8, 9).

The present work addressed patients (and the mutual relationship between the two diseases) from 2 points of view:
• That of classical medicine, pathophysiological and clinical-therapeutic, taking into consideration the existing data from specialty literature (see the general part of the thesis) and applying the personal experience to it.

• The novelty physical and mathematical modeling related to complex fluid dynamics, air (COPD) and blood (PAD) completely fitting in this category of fluids, in both normal conditions and after pathophysiological changes.

The two approach methods allowed us to explore and explain the pathophysiology of the two studied diseases from both the classical medical and physical points of view, the mathematical modeling representing an additional and very accurate argument that sustains the conclusions of this thesis. We can thus affirm that medical practice brilliantly intertwines with the rigor of exact sciences when the addressed phenomenon has a logical explanation. We also believe that the thesis opens new possibilities of further research.

Organizing the thesis in two parts: the general and personal one allowed us to properly explain the phenomena that were taken into consideration and the final conclusions.
The general part

Keeping in mind the purpose of this PhD thesis and the attempt of mathematical and physical modeling of the classical medical knowledge of sanguine rheology and the dynamics of pulmonary aerial flux, in the general part we will show the current state of knowledge in what regards the physiology, morphology and pathophysiology, and the importance of smoking in the evolution of this pathophysiology.

The personal part

The personal part of this PhD thesis tried for the first time two novelty elements:

- The first one is represented by the thoroughgoing study to understand the complex interrelations between the two major pathological entities, in whose pathophysiologies smoking plays the role of major risk factor; this study is sustained by the personal medical activity that comprised for many years the diagnosis and treatment of patients suffering from PAD; the vast majority of these patients being smokers, the initially unsuspected and later accepted contact with COPD became a concrete reality, a fact which decisively determined the choosing of the subject for this PhD thesis; the interventional cardiology
qualification allowed the complete approach of the patient suffering from PAD, the possibility of adequate therapeutic approach generating, beyond the satisfaction of well-done work, a series of novelty observational results and questions, to which attempts to answers were made, while the search of new ones is a welcome activity. From this point of view, the present work can be seen as a challenge for continuing and extending research, while also stimulating the understanding of some phenomena that are much more complex than they appear to be.

- The second one is represented by the attempt to understand and address pathophysiology of COPD and PAD from a less common point of view: the dynamics of complex fluids applied directly in the medical field. It can be said that the meeting with the distinguished figure of prof.dr. M. Agop represented a turning point in the challenge that a doctor sees in understanding the complex phenomena at micro- and macro-cellular level from a mathematical point of view, phenomena that can be explained rationally in both normal and pathological cases.
1. The dynamic approach to biological fluids

Blood and air can be considered multiphase fluids – a non–homogenous mixture of different solid particles suspended either in liquid plasma, like in the case of blood, or in gas, like in the case of air.

From this perspective both blood and air can be considered complex fluids.(36-40)

Generally, the classical models(differential ) which describe the dynamics in complex fluids are complex and ambiguous.(36,37)

However, many of the dynamics mentioned above can be classified and standardized assuming that the mechanisms of interaction between the “entities“ of complex fluids impose different spatial-temporal resolution scales and the evolution of patterns- various degrees of freedom. We are thus lead to the supposition that the “entities” of the complex fluids move on fractal curves (continuous and non-differential). Evidently, there is a multitude of complex fluids in which “entities” move along regular curves (continuous and differential). But, as we will show, the dynamics will prove reducible to the first category through cancellation of fractality.
In the present chapter we set to analyze the dynamics of blood and air as complex fluids starting from the hypothesis that the ‘’entities’’ associated with these complex fluids move on continuous and non-differential curves (fractal). The mathematical formalism is based upon non-linear dynamics. (31-33)

We observe from the beginning that blood and air, as complex fluids, are totally distinct in what regards behavior. While one is incompressible (blood), which implies that its density is constant in space and time, while the other is compressible (air), which implies variation of its density in space and time. For details on these differences references can be consulted (29,30).

II. PAD and COPD in smokers: clinical, biological, therapeutic and prognostic aspects

The clinical study in this PhD thesis was un-randomized, prospective, analytic interventional, without a default witness group and analyzed a total number of 186 patients, following the clinical, therapeutic and prognostic interrelations between PAD and COPD; The patients were split in 4 groups:

- G1: smoking patients with PAD and COPD: 58 patients (44 who were firstly recommended for cardiologic consult and 14 for respiratory one);
• G2: smoking patients with PAD without COPD: 60 patients;
• G3: smoking patients with COPD and PAD: 52 patients;
• G4: non-smoking PAD patients: 16 patients

Conclusions and discussion:

1. Demographic data: most patients are male;
2. Similarity concerning to median age in all groups;
3. Most of G1, G2 and G3 patients are smokers;
4. Significant number of patients exhibiting rest EKG changes;
5. Most common presence of degenerative valve disease in PAD patients;
6. Most common pathological IMT in smokers;
7. All smokers PAD disease patients had the same degree of arterial atherosclerotic lesions;
8. Most common positive/no conclusive ET in all groups;
9. All PAD patients with alprostadil iv treatment underwent control spirometry and prove for an improvement in spirometry parameters;
10. Concerning to the dynamic approach to biological fluids we prove that these moves on
continuous and nondifferential curves (fractal curves);

11. Fractal fluids act like a hysteretic entity with self memory;

12. Two fluids movement, one inside other, with different velocities result in biological Taylor destabilization (vortex formation at the borders level);

13. It can be seen a stop effect;

14. Auto similarity in transfer process for biological fluids can be assimilate with a hologram.
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