Proposal for a new COST Action

COST B26

OBSTRUCTIVE SLEEP APNEA

Action Proposer: Maria Rosaria BONSIGNORE
Istituto di Medicina Generale e Pneumologia
University of Palermo
Ospedale V. Cervello
Via Trabucco 180, 90146 Palermo, Italy
Tel: +39-091-6802714 (work)
+39-328-7538815 (cell phone)
Fax: +39-091-6882165
E-mail: work: marisa@ibim.cnr.it

COST National Coordinator: Mr. Gioacchino FONTI
Ministero Istruzione Università Ricerca
Research Department
Piazza J.F. Kennedy, 20
00144 Rome
ITALY
Tel: +39 06 58497639
Fax: +39 06 58497368
E-mail: gioacchino.fonti@murst.it

TC-MH rapporteur: Prof. Jose ROCA TORRENT
Hospital Clinic Barcelona
Servicio de Neumología
C/ Villarroel 170
08036 Barcelona
Tel: +34-93 2275540
Fax: +34-93 2275455
E-mail: jroca@clinic.ub.es
For the implementation of a European Concerted Research Action designated as

COST B26

OBSTRUCTIVE SLEEP APNEA

The signatories to this 'Memorandum of Understanding', declaring their common intention to participate in the concerted Action referred to above and described in the 'Technical Annex to the Memorandum', have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 400/01 'Rules and Procedures for Implementing COST Actions’ the contents of which the Signatories are fully aware of.

2. The main objectives of the COST Action B26 are:

   - To assess the role of the Obstructive Sleep Apnea Syndrom (OSAS) as a possible cause of increased cardiovascular risk.

   - To coordinate studies on pathogenetic mechanisms of increased cardiovascular risk of OSAS (i.e., inflammation, oxidative stress, endothelial dysfunction, metabolic derangements, altered autonomic control associated with exposure to intermittent hypoxia).

3. The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EURO 10 Million in 2004 prices.

4. The Memorandum of Understanding will take effect on being signed by at least five Signatories.

5. The Memorandum of Understanding will remain in force for a period of four years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter 6 of the document referred to in Point 1 above.
A. Background

During sleep, the tone of upper airway dilator muscles normally decreases, favouring collapse of the nasopharyngeal region of the upper airway. Upper airway narrowing is responsible for snoring, whereas complete closure causes apneic events associated with persistence of respiratory movements. Airflow obstruction during sleep can be partial (hypopnea) or complete (apnea), and is resolved by an arousal, i.e. a short interruption of sleep, which re-establishes muscle tone and airway patency. As the subject goes back to sleep, however, upper airway obstruction can reappear, and in the most severe cases the cycle is repeated up to hundreds of times during a single night.

In normal adults, episodes of upper airway obstruction may occur during sleep, but they are fewer than 5 per hour of sleep, i.e. the Apnea Hypopnea Index (AHI) is < 5/h. In the general adult population, 9% of men and 4% of women show an AHI >5/h, and 4 and 2%, respectively, also refer clinical symptoms of the obstructive sleep apnea syndrome (OSAS). Sleep apnea is particularly frequent in overweight or obese subjects, suggesting that its prevalence may increase in the near future due to a sedentary lifestyle in Western countries.

The main clinical features of OSAS include a history of loud snoring (indicating vibration of soft tissues during upper airway obstruction), a variable degree of impairment of daytime function (excessive daytime sleepiness secondary to sleep fragmentation) and several alterations secondary to nocturnal oscillations in oxygen content of arterial blood. These changes jointly cause profound alteration of autonomic nervous system activity, by increasing sympathetic and decreasing vagal activity. During sleep, hypertensive peaks occur after each apnea. In addition, about 50% of patients with OSAS are hypertensive during wakefulness, and often show a poor response to antihypertensive treatment. OSAS is included as a potential cause of increased blood pressure in the most recent guidelines on management of hypertension. Besides its causal relationship with systemic hypertension, OSAS has been strongly implicated as a risk factor for coronary artery disease and stroke. Uncontrolled studies indicate that cardiovascular mortality is increased in patients with untreated OSAS. In summary, the major adverse health consequences of OSAS in the long-term appear to involve the cardiovascular system, but firm evidence is still lacking and pathogenetic mechanism(s) are to some extent unclear.

The “gold standard” treatment for OSAS is nasal continuous positive airway pressure (CPAP). CPAP application during sleep, after titration of the appropriate pressure level, stabilises upper airway walls and patency, normalises sleep structure, respiration and arterial oxygenation, and prevents sympathetic overactivity and blood pressure swings during sleep. The long-term effects of CPAP treatment on cardiovascular risk are still uncertain. Uncontrolled studies have reported that cardiovascular morbidity and mortality in treated patients are similar to those recorded in the general population. However, the variable degree of patient compliance to treatment constitutes a major problem in assessing the effects of CPAP. Other treatment options exist (upper airway surgery and oral appliances) aimed at increasing the dimensions of the nasopharyngeal tract of the upper airways. Obesity is a major and well-known risk factor for cardiovascular disease. Consequently, the association between OSAS with obesity complicates studies on the independent impact of OSAS on the cardiovascular system. The effects of OSAS treatment on cardiovascular risk are currently unproven although a moderate blood pressure reduction has been documented in treated patients. Other
additional factors may play an important role in this interaction. For instance, metabolic alterations (insulin resistance, leptin resistance), increased concentrations of pro-inflammatory mediators (interleukin 6 and C reactive protein) and oxidative stress have been found in OSAS patients, but the relative roles of OSAS and obesity in causing these changes are unclear. Ongoing studies on the role of genetic factors are complicated by the complexity of OSAS phenotype. Studies in large patient samples are therefore necessary to clarify the role of OSAS and obesity in the pathogenesis of cardiovascular and metabolic alterations as possible causes of accelerated atherogenesis, as well as the effects of CPAP treatment.

To study the role of OSAS as a cardiovascular risk factor, it is particularly timely and necessary to develop a European network on OSAS, in order to promote collaboration between Sleep Laboratories and attain a critical mass of data for assessment of the incidence of cardiovascular events during follow-up in treated and untreated OSAS patients. This network includes groups involved in clinical and basic research to provide new insights into pathogenetic mechanisms and improve our approach to patient management. Currently, the working group on sleep disordered breathing of the European Respiratory Society (ERS) promotes cooperation among laboratories, but contacts are restricted to ERS Annual Meetings, and for this reason, are inadequate to generate a continuous cooperation between researchers. The COST Action B26 aims at establishing a permanent network among outstanding groups actively contributing to studies on OSAS in different European countries, in order to pursue advances in clinical and basic research on OSAS and cardiovascular risk.

B. Objectives and benefits

The main objectives of the COST Action B26 are:

(i) to assess the role of OSAS as a possible cause of increased cardiovascular risk. Collaboration among different countries will provide a critical mass of data in both untreated and treated patients, and result in the development of guidelines on preventive measures;

(ii) to coordinate studies on pathogenetic mechanisms of increased cardiovascular risk of OSAS (i.e., inflammation, oxidative stress, endothelial dysfunction, metabolic derangements, altered autonomic control associated with exposure to intermittent hypoxia). These studies will highlight possible factors susceptible to correction by therapy.

Secondary objectives are to promote exchanges between groups in the following fields:

(i) diagnosis of OSAS and patient management: guidelines exist on diagnosis of OSAS, but evaluation of cardiovascular risk factors is not routinely performed in OSAS patients. The joint effort of several groups will be helpful in setting up a useful and cost-effective European protocol to longitudinally evaluate cardiovascular risk in OSAS patients;

(ii) excessive daytime somnolence (EDS) and medico-legal implications of OSAS: Problems still exist on the assessment of EDS in OSAS. OSAS increases the risk of car accidents, but legislation addresses the problem in different ways throughout Europe. A European Network will contribute in developing guidelines and promotion of their application in European countries. In this respect, the COST Action B26 will be complementary to the ongoing FP6 Integrated Project on sleepiness entitled: “Advanced sensor development for attention, stress, vigilance and sleep/wakefulness monitoring” (acronym: SENSATION, project number: 507231);
(iii) establish a common protocol to be adopted by all participating Centres for data collection at baseline and during clinical follow-up of treated and untreated OSAS patients, in order to cross-sectionally and prospectively assess the association between OSAS and cardiovascular morbidity in a sufficiently large patient sample representative of the European population.

C. Scientific programme

To reach the objectives the following activities will be undertaken:

(i) establish a common protocol to be adopted by all participating Centres for baseline data collection and during clinical follow-up of treated and untreated OSAS patients. This is in order to assess both cross-sectionally and prospectively the association between OSAS and cardiovascular morbidity in a sufficiently large patient sample representative of the European population;

(ii) create a European working group on epidemiology and genetics of OSAS and its complications, coordinating studies in existing cohorts in order to possibly identify markers of increased risk;

(iii) assemble and publish on a dedicated website, a directory of European laboratories active in the diagnosis and treatment of OSAS and its cardiovascular consequences. As a result investigators working on similar or complementary clinical and research issues will be able to establish cooperation and exchanges. Other researchers will also get the information and, thus, be able to communicate with the identified groups so providing the basis for a wider European Network;

(iv) establish a list of reference laboratories, by means of the above directory and the knowledge of published and in press papers and progress activities, for specific research issues on cardiovascular complications in OSAS. Investigators from these laboratories will be able to spread information on recent key findings, relevant publications, and diagnostic applications through the organisation of specific workshops;

(v) establish and up-date guidelines for diagnosis of OSAS, evaluation of cardiovascular risk, and medico-legal implications of daytime somnolence. The aim is to publish the outcome in the international literature and provide related joint studies.

General and specific topics will also be addressed. Two main scientific areas are proposed:

- Clinical area: controlled follow-up studies in treated and untreated OSAS (longitudinal assessment of risk for cardiovascular complications and effects of treatment in a large European patient sample); development of a protocol to assess cardiovascular risk in OSAS patients during diagnosis and follow-up; evaluation of daytime somnolence and medico-legal implications.

- Research area: studies on the pathogenetic mechanisms of increased cardiovascular risk in OSAS (inflammation, oxidative stress, endothelial dysfunction, metabolic derangements associated with exposure to intermittent hypoxia); epidemiology and genetics of OSAS.
D. Organisation

The Action is planned for four years. The first meeting of the Management Committee (MC) will further define the aims: directory, workshops, scientific cooperation, guidelines for diagnostic services.

The MC Chair will aggregate all the information provided by MC members and will assemble the directory of the European laboratories and scientists involved in research on cardiovascular complications of OSAS. The directory will appear on a web page dedicated to this COST Action B26 and aimed at spreading information on it. The MC Chair will be in charge of updating the directory, communicating the workshops which will be organised and the documents/guidelines produced by the COST network.

Based upon an inventory of the activities and interests of the participating groups, the initial meeting of the MC will specify the clinical and research areas described in the scientific programme, and will indicate how (what and by whom) implementation will take place. The activities will be organised under three major Working Groups (WGs) on:

- WG 1: Cardiovascular complications in OSAS: pathogenetic mechanisms and markers of increased cardiovascular risk.
- WG 2: Daytime somnolence and medico-legal implications of OSAS
- WG 3: Epidemiology and genetics of OSAS.

0.5-1 YEAR
General meeting of WG1 on cardiovascular complications of OSAS ("reference" WG): setting-up a common protocol and planning of clinical follow-up of OSAS patients; identification of investigator subgroups studying mechanisms of cardiovascular complications (e.g. inflammation, oxidative stress, endothelial dysfunction, metabolic derangements, autonomic dysfunction).

First meeting of the WG2 on daytime somnolence and medico-legal implications of OSAS
First meeting of the WG3 on epidemiology and genetics of OSAS.
Communication on the web site of all the proposals and news from the working groups.
First release of the directory.

1/1.5-2 YEARS
Integrated Meeting of all WGs: progress report on clinical follow-up and research activities. Discussion on progress in the development of clinical guidelines on diagnostic and medico-legal aspects of OSAS. Release of up-dated directory.
Communication on the web site of the agenda of future activities.

2/2.5-3 YEARS
Meeting of the each of the WGs: release of progress reports.
Integrated Meeting of all WGs: discussion of progress reports and planning for release of guidelines.
Release of updated directory.

3-4 YEARS
Meeting of WG1: Release of guidelines on diagnostic protocols for cardiovascular complications in OSAS. Statement papers on results, clinical usefulness of identified biomarkers, and future perspectives.
Meeting of WG2: Release of guidelines on medico-legal implications
Meeting of WG3: Statement paper on state of the art of European research on epidemiology and genetics of OSAS and future perspectives.

All documents will be published in European medical journals dedicated to Respiratory and possibly Cardiovascular Medicine; they will be translated in different languages and further disseminated at the National level (care of National participants).

Plenary “assembly” to discuss:

- longitudinal data collected during the COST Action B26, and planning of future Actions to pursue and continue clinical follow-up
- outcome of research projects and possible future development

The results of the clinical follow-up study and of basic research projects developed during the Action will be published in international journals. A final document summarising the aims and results of the Action will be published on the website and in journals of different medical specialties (for example Sleep Medicine, Cardiology, Epidemiology), in order to increase the visibility of the Action and spread its results to the medical community.

E. Timetable

A summary of the timetable is given in the figure below. Bars indicate planned meetings of MC (light gray) and WGs (blue, green and pink, respectively).
F. Economic Dimension

Scientists from the following 14 COST States have been actively involved in the preparation of the Action and have expressed interest in active participation. These are: Belgium, Finland, France, Germany, Israel, Ireland, Italy, Latvia, Lithuania, Poland, Slovak Republic, Spain, Sweden, United Kingdom.

On the basis of estimates provided by the participating experts and taking into account coordination costs, the overall cost of the activities to be carried out within the framework of the COST Action B26 has been estimated in 2004 prices between EURO 10 Million.

This estimate is valid under the assumption that all countries mentioned above, but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

G. Dissemination Plan

Dissemination will be achieved through the following activities:

- Publication in international journals together with related joint studies generated within the network of European guidelines for diagnosis of OSAS, evaluation of cardiovascular risk in OSAS patients, and medico-legal implications of daytime somnolence.

- Diffusion of basic information on OSAS and its cardiovascular consequences by a section of the website dedicated to patients and their relatives and by documents summarising the results of the Action targeted at the medical community, the patient community and the public opinion.

- COST Action B26 meetings will be planned in conjunction with European or other National/International Medical Conferences (for example, those organised by the European Respiratory Society, the European Sleep Society, or the European Society of Cardiology). This strategy will increase the visibility of the Action at a multidisciplinary level.

- Elaboration and diffusion on the web site of a directory of European laboratories, groups and individual researchers working on OSAS and cardiovascular risk for purposes of diagnostic activity or basic research.

- Elaboration of a list of reference labs working on mechanisms of cardiovascular complications in OSAS. Investigators of these laboratories will be in charge of spreading information on recent key findings, relevant publications, diagnostic applications through organisation of specific workshops.

- Publication of annual reports on the web site.
COST B26

Obstructive Sleep Apnea

ADDITIONAL INFORMATION
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PART 2 : ADDITIONAL INFORMATION

1. Added Value of the Action

The COST Action B26 will further European clinical and basic research on OSAS by making it more organised and competitive, and by establishing cooperation with other European research networks on health problems such as obesity, diabetes, and cardiovascular disease. Cooperation can also be extended to networks on OSAS operating in non-COST Countries, for example, in the US. The COST Action B26 will increase the perception of OSAS as a clinically relevant problem in the medical community, and will act as a powerful means to attain harmonisation of diagnostic and therapeutic procedures in European public health. This will be accomplished through the production of guidelines and statement papers to be published in international medical journals. These publications will also be useful for policy making institutions, such as the European Parliament, in order to promote preventive and therapeutic measures for health consequences of OSAS.

Endorsement of the COST Action B26 on OSAS by the European Respiratory Society (and possibly other European professional/scientific societies) will increase the visibility of the network. Synergies with other European organisations (EC, ESF, etc) will help disseminate the results of the Action at the patient and public opinion levels, by producing simplified documents on the dangers to health posed by OSAS and the advantages provided by treatment. In addition, OSAS patients and relatives will benefit from a website dedicated to this disease, where they can find updated information on sleep disordered breathing provided by institutional sources. The network on OSAS will stimulate possible innovations by providing new ideas and promoting collaboration with industrial partners involved in diagnostics and treatment of OSAS.

2. Proposal by:

Proposal by: Maria R. Bonsignore (Palermo, Italy), marisa@ibim.cnr.it or m.bonsignore@unipa.it

Participants adhering to the proposal (14 countries)

Belgium  Wilfried De Backer (Antwerp), dbacker@uia.ua.ac.be
         Daniel Rodenstein (Brussels), rodenstein@pneu.ucl.ac.be
Finland  Olli Polo (Tampere), ollipolo@utu.fi
France   Patrick Levy (Grenoble), PLevy@chu-grenoble.fr
Germany  Konstanze Diefenbach (Berlin), konstanze.diefenbach@charite.de
         Ingo Fietze (Berlin), ingo.fietze@charite.de
         Thomas Penzel (Marburg), penzel@Mailer.Uni-Marburg.DE
         Richard Schulz (Giessen), Richard.Schulz@innere.med.uni-giessen.de
Israel   Lena Lavie (Haifa), lenal@technix.technion.ac.il
         Peretz Lavie (Haifa), plavie@tx.technion.ac.il
Ireland  Walter McNicholas (Dublin), walter.mc nicholas@ucd.ie
Additional Information