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EDITORIAL

The genetic and cardiovascular aspects of obstructive sleep apnoea/hypopnoea syndrome

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In November 2006, the COST B26 action on cardiovascular disease in obstructive sleep apnoea/hypopnoea syndrome (OSAHS) convened a symposium in Copenhagen (Denmark). The symposium was an attempt to bring experts together to define the direction in which the fast pace of change in the fields of molecular biology and genetics was pushing frontiers, particularly in the context of cardiovascular diseases and OSAHS. An upcoming series that will be published over the next 6 months in the *European Respiratory Journal* (*ERJ*), presents some of the key papers from the symposium. The first paper in the series, by MACLEOD *et al.* [1], introduces the importance of meticulous design, data collection and storage in studies of complex disease, using the example of Generation Scotland. The paper serves as the background for further contributions to the series, which continue with a discussion of the difficulties in phenotyping and, by inference, the difficulties inherent to genotyping such a complex disorder as OSAHS [2]. The epidemiological aspects of OSAHS and sleep-disordered breathing (SDB) are discussed separately [3]. The sequelae of OSAHS are considered in detail, particularly the molecular biology of oxidative stress mechanisms [4], as well as inflammatory pathways [5] which determine the comorbidities increasingly recognised in the context of SDB. Finally, the series concludes with evidence for and against the coexistence of and increased propensity of developing metabolic syndrome, hypertension and insulin resistance in SDB with and without hypoxaemia [6].

DESIGN OF GENETIC STUDIES IN CARDIOVASCULAR DISEASE AND OSAHS PRINCIPLES AND PRACTICE

In the first paper of the series, MACLEOD *et al.* [1] demonstrate that when studying genetic aspects of complex diseases such as hypertension and OSAHS, good sample and data management is necessary to ensure that the data collected are stored accurately and efficiently, and passed through the process of analysis in an orderly manner. In order to be able to collect information on a complex trait, increasingly larger cohorts are required for adequate power and subsequent replication of findings. This is important since small genetic or molecular changes can effect large changes that are only recognisable within a large population. Genetic biobanking is becoming increasingly prevalent and the principles of storage of data as well as the ethical issues associated with it are described in detail. MACLEOD *et al.* [1] use the example of the Generation Scotland project, which has been successfully run for the last 5 yrs with its centre located in Edinburgh (UK).

THE PHENOTYPE AND GENOTYPE IN OSAHS

Numerous problems arise when trying to define the phenotype of OSAHS. OSAHS can be broken down into intermediate phenotypes, which in themselves can be complex. This inherent complexity is reflected in the number of highly contradictory findings in both genome-wide linkage-based analyses and candidate gene studies to date. On an almost bimonthly basis, a new single nucleotide polymorphism (SNP) association is tested in a small group of patients with OSAHS, variably defined according to local guidelines. To date, there has been no consistent replication of findings of any of the studies, thus attracting criticism of being underpowered, poorly controlled and poorly phenotyped. In order for us to move closer to the genetic basis of understanding OSAHS in the general population, we must make cohesive and constructive efforts towards developing international and national multicentre trials, with collections of large data banks from the populations being studied.

A problem that has not been fully appraised in the scientific community is the number of ethical issues raised by widespread use of genetic testing in clinical practice. There is evidence to show that despite the recent increase in media publicity about genetic research, the level of knowledge in patients with chronic diseases such as asthma has not undergone a parallel increase [7]. Important aspects regarding this are discussed by MACLEOD *et al.* [1], including data confidentiality, consent and reporting of results to patients. Genetic testing has given rise to other issues such as the possibility of stigma and challenging cultural and social attitudes. There is wide scope for misuse and questions arise if data are requested, for instance, by medical insurance companies. Various countries have undertaken steps disparately towards finalising legislation regarding this problem [8].

THE EPIDEMIOLOGY OF OSAHS

OSAHS appears to be a complex polygenic disease and, as described by JENNUM and RIHA [3], this throws hurdles in the path of epidemiological studies of this area. A number of excellent studies in the last two decades have attempted to

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define the prevalence of SDB with and without symptoms in various populations [9–14]. Such large population studies are laborious, time-consuming and often restricted by the technology available at the time to perform them in the most cost-effective manner. Definitions of OSAHS can be adapted to suit local conditions and local prejudices and paradigms (often economically motivated). The generalisability of these findings is therefore limited.

OSAHS within the general population has been found to be associated with a number of conditions, such as polycystic ovarian syndrome and the metabolic syndrome; it is more prevalent in patients with type 2 diabetes mellitus and has also been shown to be a risk factor for the development of cardiovascular disease and hypertension [15]. Technology to assess the disorder has at times been limited and there are very real problems of screening large populations. What is currently unknown is whether the OSAHS phenotype remains static throughout life and is part of a spectrum of diseases or whether it develops. There is a very real lack of longitudinal studies in either adult or paediatric OSAHS.

MOLECULAR MECHANISMS OF CARDIOVASCULAR DISEASE IN OSAHS: THE ROLE OF OXIDATIVE STRESS

While OSAHS is associated with a diverse range of pathophysiological features ranging from sleep fragmentation and daytime sleepiness to recurring episodes of apnoea-associated oxygen desaturation, there is growing evidence that intermittent hypoxia is a key feature in the cardiovascular pathophysiology of the disorder because of the associated intermittent re-oxygenation. This latter feature has been compared to reperfusion injury and predisposes to oxidative stress with the production of increased quantities of reactive oxygen species (ROS) [16]. In their review, LAVIE and LAVIE [4] examine the role of oxidative stress in initiating cardiovascular consequences in OSAHS. While ROS serve an important physiological role relating to signal transduction and as second messengers in many signaling pathways, excessive ROS production can damage cellular components and various biomolecules, such as lipids, proteins, DNA and carbohydrates, and by that alter their biological functions.

LAVIE and LAVIE [4] review the evidence for oxidative stress in OSAHS, which is based on: the demonstration of increased ROS production by leukocytes taken from patients with OSAHS and in rodents exposed to intermittent hypoxia; and also by the demonstration of reduced ROS production following continuous positive airway pressure (CPAP) therapy. Furthermore, evidence of oxidation of various macromolecules, particularly lipid peroxidation, in OSAHS provides additional evidence in support of oxidative stress. The demonstration of oxidative stress in OSAHS opens up the possibility of novel therapeutic approaches and it is notable that treatment with the xanthine oxidase inhibitor, allopurinol, or by the antioxidant vitamin C, has been reported to be associated with improved endothelial function in patients with OSAHS.

LAVIE and LAVIE [4] also emphasise that, in addition to intermittent hypoxia and re-oxygenation, there is evidence of ROS activation in other intermediate mechanisms associated with OSAHS, such as sympathetic excitation and obesity, and also in other disorders that commonly occur in patients with OSAHS, such as hypertension, hyperlipidaemia and diabetes. Thus, the relationship between oxidative stress and OSAHS is complex and it may be difficult to separate out the respective contribution of different mechanisms, particularly in clinically based studies where careful patient selection and matching for confounding variables become particularly important.

CARDIOVASCULAR DISEASE IN OSAHS: THE ROLE OF HYPOXIA AND INFLAMMATION

The mechanisms underlying cardiovascular disease in patients with OSAHS are still poorly understood but are likely to be multifactorial, including sympathetic nervous system overactivity, selective activation of inflammatory pathways, oxidative stress, vascular endothelial dysfunction and metabolic dysregulation, with the latter particularly involving insulin resistance and disordered lipid metabolism. Some of these mechanisms are likely to have a genetic basis. The development of cell culture and animal models of intermittent hypoxia in recent years have allowed investigation of the role of intermittent hypoxia in the activation of inflammatory mechanisms and the development of atherosclerosis in OSAHS. In their review, GARVEY *et al.* [5] highlight the role of intermittent hypoxia in the pathophysiology of cardiovascular complications in OSAHS through activation of pro-inflammatory pathways. They discuss the hypoxia-sensitive transcription factors that may contribute to the inflammatory and cardiovascular consequences of intermittent hypoxia. The transcription factors hypoxia inducible factor-1 and nuclear factor (NF)-κB appear to play a key role [17] and recent discussion [5] indicates significant interdependence between these two hypoxia-sensitive pathways. GARVEY *et al.* [5] review the data garnered from translational studies involving cell culture and animal models of intermittent hypoxia, which complement data from studies of OSAHS patients. GARVEY *et al.* [5] discuss the effects of intermittent hypoxia in specific tissue types, with the aim of identifying the target organs of intermittent hypoxia in OSAHS. Finally, they review the therapeutic potential of targetting inflammatory mechanisms in the management of the disorder.

The inflammatory responses directly related to OSAHS must be distinguished from those found in obesity-related inflammation. Obesity, particularly visceral adiposity, is associated with chronic low-grade inflammation, and adipocytes express high levels of inflammatory cytokines such as tumour necrosis factor (TNF)-α and interleukin (IL)-6 [18]. Induction of these inflammatory cytokines in adipose tissue can also have further downstream metabolic effects often associated with OSAHS. The role of hypoxia in regulating these effects in adipose tissue is largely unknown and represents an important area for future studies. Since obesity is likely to be associated with diminished vascular supply to adipose tissue, the possibility of hypoxia affecting these tissues in patients with OSAHS is high.

METABOLIC SYNDROME AND OSAHS

Many studies have reported an independent association of OSAHS with several components of metabolic syndrome (MS), particularly insulin resistance and abnormal lipid metabolism, and this association may further increase cardiovascular risk since MS is recognised as a risk factor for cardiovascular

morbidity and mortality. In their review, LÉVY *et al.* [6] discuss the relationship between MS and OSAHS, and particularly the interaction with sleep restriction and obesity.

Epidemiological studies suggest that OSAHS is independently associated with alterations in glucose metabolism and places patients at an increased risk of the development of type 2 diabetes [19, 20]; however, the confounding effect of obesity in this association has not yet been fully addressed. While data from the Sleep Heart Health Study [19] indicate that sleep apnoea severity was associated with the degree of insulin resistance after adjustment for obesity, longitudinal data from the Wisconsin Sleep Study Cohort [20] showed that obstructive sleep apnoea at baseline was not a significant predictor of the development of diabetes over a period of 4 yrs, after adjusting for obesity. Furthermore, the possibility that sleep disruption *per se* as a consequence of OSAHS is responsible for insulin resistance is an additional potential confounding factor. Reports that obesity is associated with sleep restriction further add to the complexity of these relationships and emphasise the difficulty in identifying truly independent relationships [21–23].

Leptin is an adipocyte-derived hormone that regulates body weight through the control of appetite and energy expenditure. While several studies have reported that OSAHS is associated with hyperleptinaemia, adjustment for obesity and visceral fat distribution was inconsistent. Furthermore, a report from the Cleveland family study also demonstrated body mass index (BMI) to be an important confounding factor in the relationship between OSAHS and leptin levels [24]. Thus, the possibility of an independent relationship of leptin and other adipocytokines, such as adiponectin and ghrelin, to OSAHS requires further investigation.

CONCLUDING REMARKS

While major progress has been made in understanding the pathophysiology and clinical consequences of obstructive sleep apnoea/hypopnoea syndrome, considerable gaps remain. Recent reports have highlighted the broad range of intermediate mechanisms that contribute to the development of cardiovascular disease in obstructive sleep apnoea/hypopnoea syndrome patients, and emphasise the genetic aspects of these relationships. The complex pathophysiology of obstructive sleep apnoea/hypopnoea syndrome and the broad range of associated disorders indicate that carefully designed large-scale prospective studies will be required to identify independent relationships with confidence. Furthermore, animal models are likely to provide the best *in vivo* setting to evaluate the role of specific intermediate mechanisms in disease pathogenesis.

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