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PHYSIOLOGICAL REVIEW

Understanding sleep-disordered breathing through mathematical modelling

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SUMMARY

Recent studies have uncovered high prevalence of undiagnosed sleep-disordered breathing, and its linkage to metabolic or cardiovascular disorders which represent increasing health hazard. However, the mechanistic links behind these disorders as well as their contribution to the experimental observations and treatment responses remain poorly understood. Therefore, the screening of clinical measurements still relies upon relatively simple diagnostic features, such as signal averages or event frequencies, which may represent suboptimal or surrogate markers of the underlying abnormality. Consequently, most patients are being treated with general therapies regardless of the cause of their key dysfunction. Combining experimental measurements with mathematical modelling has the potential to provide mechanistic insights into the individual factors underlying the disease progression, which may finally enable tailored treatment alternatives for each patient. This review depicts a number of modelling approaches to elucidate sleep-related dysfunctions of the human respiratory system, and how these models are being used to translate the measurements first into new ideas and then into testable hypotheses. Such model-based investigations can provide systematic strategies towards better understanding, predicting or even preventing these dysfunctions. Along with the brief description of the modelling approaches, we discuss their relative merits and potential implications especially for clinical research.

Introduction

Obstructive sleep-disordered breathing (SDB) is a common condition, which manifests in a spectrum of conditions ranging from simple snoring and airflow limitation through partial upper airway collapsibility and hypopnea to the obstructive sleep apnea syndrome (OSAS). A number of clinical conditions related to SDB are nowadays occurring with greater frequency as the population ages and becomes more obese in many countries. While it was earlier estimated that 5% of the adults in Western countries suffer from the symptoms of OSAS, such as excessive daytime sleepiness,[1] the recent reports suggest that as many as one in four American adults are at high risk for OSAS.[2] In addition to the patients having symptoms of OSAS, recent studies have linked also the milder forms of SDB with increased likelihood of hypertension and other cardiovascular consequences.[3–5] This cluster of conditions shares also many risk factors with the metabolic syndrome.[6–8] Moreover, childhood SDB is associated with neurophysiological deficits of memory, learning and executive function.[9] Considering these serious and lifelong health consequences, there is a critical need for novel strategies to increase our understanding of the pathophysiology of SDB, and its links to the related disorders, enabling their early detection and effective treatment.

The development of SDB depends on the complex interplay of multiple anatomic and physiological factors but the mechanisms behind these factors or their impacts on the type or degree of the disorder, experimental observations or on the treatment responses remain poorly understood. While the key regulatory mechanisms involved in the respiratory control are well-established,[10] as well as the main causes leading to SDB,[11,12] what is lacking is an experimental-analytic framework, consisting of a simple measurement setup and formal decision rules, that could efficiently employ this body of knowledge in transforming the experimental measurements into clinical information. Although current experimental techniques enable overnight monitoring of multiple signals in

Abbreviations: AHI, apnea–hypopnea index; CO_2, carbon dioxide; CPAP, continuous positive airway pressure; $EtCO_2$, end-tidal partial pressure of CO_2; HbA1c, glycosylated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IMT, carotid artery intima–media thickness; NMD, nitroglycerin-mediated dilatation; O_2, oxygen; ODI, oxyhemoglobin desaturation index; OSAS, obstructive sleep apnea syndrome; $PaCO_2$, arterial partial pressure of CO_2; SaO_2, oxyhemoglobin saturation; SDB, sleep-disordered breathing; $TcCO_2$, transcutaneous partial pressure of CO_2.

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a research setting, the complexity and cost of these methods and their possible impact on sleep and the system may limit their usage in clinical routine. Moreover, the conventional diagnosis screening is based on the identification of respiratory-related events in these measurements, such as episodes of apnea, hypopnea or arousal, but such indices alone can provide only limited information about the various mechanisms responsible for producing these events. Accordingly, the emphasis of the diagnostic procedures should move from complicated measurement of the secondary events towards determination of the primary dysfunction in a given individual using minimally invasive measurement techniques.

Mathematical models provide us a quantitative means for understanding the dynamic behaviour of complex physiological controlling systems, facilitating the mechanistic interpretation of the experimental measurements and the prediction of clinically important events in the systems function. Mathematical modelling has successfully been used, for instance, in explaining the occurrence of periodic breathing in patients with cardiac symptoms as a result of instability of the respiratory control system.[13,14] Besides providing mechanistic insights into the disease pathogenesis, modelling can be used to suggest novel hypotheses, predict clinically relevant outcome variables, or even to test the efficiency of different treatment settings.[15,16] This may lead to novel and exciting physiological paradigms which can in turn contribute to the development of efficient treatment alternatives to prevent these conditions. For diagnostic testing, models can also help us to choose optimal experimental setup by revealing the various disturbances underlying the development of the medical conditions and by suggesting the most effective measurements for their early detection. Given the rapidly growing incidence of SDB, there is an increasing need for such automated tools to facilitate clinical decision-making that could provide a cost-effective support to conventional experimental studies.

This review describes how mathematical modelling can be used to study the operation of the human respiratory control system in health and disease. Our particular focus is on the dynamic behaviour of the system during transition from wakefulness to sleep, and on those system dysfunctions that are implicated in the development of SDB and its related conditions. As substantial efforts have been devoted to the topic over the past 40 years, only representative examples of different modelling approaches can be surveyed here, with an emphasis on those model-based studies that target at addressing clinical questions, rather than mathematical or computational issues only. After having introduced the necessary modelling terminology and techniques in the context of modelling the respiratory control system during sleep, two concrete case studies are given that demonstrate how models can identify important features from overnight experimental measurements, including non-invasive recording of respiratory airflow and carbon dioxide levels, and how these features can be used to predict respiratory, metabolic and cardiovascular abnormalities. Potential treatment options based on the model predictions will also be discussed in the course of these two particular case studies. Finally, we highlight some challenges in the field and offer our personal view of the key future trends and developments in the model-based analysis of SDB.

Modelling the human respiratory control system during sleep

A mathematical model[a] can be broadly regarded as a quantitative description of an observed system or its particular process, which mimics those aspects of the real behaviour that enable useful predictions to be made. Mathematical modelling as a systematic tool to test new ideas and make hypotheses about the real word phenomena has a long and successful record especially in the physical sciences. Recently, modelling has increasingly being used also in many fields of the biomedical sciences, especially in biomedical engineering and systems biology. Due to the complexity of many biological processes and our improved possibilities to make high-throughput measurements at multiple levels of a system, models have become indispensable tools in the integration, analysis and interpretation of the experimental measurements. At the same time, powerful computing capacity has made it possible to build realistic models of biological systems that can be run on standard computers to simulate these processes in quantitative terms. This is illustrated by the possibility of building meta-models, in which different model components are coupled together to predict macro-level behaviour. Beyond computer simulations, model predictions can lead – sometimes after a great deal of effort – to a hypothetical mechanism that is able to explain the observed behaviour and can be tested with subsequent experimentation. In addition to providing better understanding of the system's properties, e.g., its many dysfunctions, perhaps the most exciting potential comes from the possibility to design rational strategies to modify a pathologic behaviour of the system back to its normal state.

Due to its high inherent complexity and medical importance, the many properties of the human respiratory control system have been a topic of a large number of modelling studies, varying both in their abstraction level and modelling approach. These modelling choices are typically made on the basis of the specific physiological application, that is, whether one is interested in the disease pathogenesis, its diagnosis or treatment. Of the various modelling approaches, one should choose the approach that can best address the question under analysis, and often the most useful models are not necessarily those involving most mathematical sophistication or computational complexity. So-called descriptive models aim to reveal relationships among the experimental measurements and other information (referred globally to as features), and their contribution to a particular clinical outcome. Typical examples include using stepwise linear regression modelling to select an independent subset of anatomic and other features that could account for most of the individual variability in SDB, e.g., in terms of the observed apnea–hypopnea index (AHI).[17] A related modelling approach determines those features only that can predict the correct AHI-class of a new subject as accurately as possible by exploiting possible non-linear relationships between the features in predictive models.[18] These models and features can then be used, e.g., for prioritizing patients for polysomnographic sleep studies.[19] More information on the descriptive and predictive modelling approaches can be found from related books.[20]

Compared to descriptive modelling, mechanistic models have typically a rather different objective of providing mechanistic insights into the behaviour of the respiratory system under different physiological or pathophysiological conditions. Traditional applications include finding conditions under which the respiration becomes stable or unstable, and the most important factors affecting the occurrence and type of the periodic breathing.[21,22] These early modelling works have revealed, e.g., that the control system instability may originate from prolonged circulatory times or disturbed chemosensitivity to hypercapnia and hypoxia. Such findings can have direct implications for medical problems, such as congestive heart failure,[23,24] or sudden infant death syndrome.[25,26] Model-based approaches to understanding the nature of periodic breathing, especially in the context of central SDB, have extensively been described in a recent review.[14] In general, the mechanistic modelling approach benefits from the

[a] Underlined terms are further defined in a Glossary of terms at the end of the text.