Obstructive Sleep Apnea in Adults
Obstructive Sleep Apnea in Adults

Relationship with Cardiovascular and Metabolic Disorders

95 figures in color, 37 tables, 2011
To my wife Liora and
my children Alexandra and David
for their patience and tolerance

In memory of my mother and father
Disclosure Statement
A.L. has participated in speaking engagements for Linde Healthcare and Pfizer. He has no financial conflicts of interest with the subject matter discussed in this book.
## Contents

Preface ................................................................. XV
Acknowledgements .................................................. XVI

Chapter 1
Obstructive Sleep Apnea in Adults: Epidemiology, Clinical Presentation, and Treatment Options ......................... 1

1 Definitions .......................................................... 3

2 Prevalence and Incidence of Obstructive Sleep Apnea ................. 5

3 Risk Factors for Obstructive Sleep Apnea ................................ 7
3.1 Overweight, Obesity, Metabolic Syndrome and Alterations in Glucose Metabolism ........................................ 7
3.2 Age ..................................................................... 8
3.3 Gender .................................................................. 8
3.3.1 Menopause, a Risk Factor for Obstructive Sleep Apnea ....... 8
3.3.2 Testosterone Levels and the Risk of Obstructive Sleep Apnea ... 9
3.3.3 Polycystic Ovary Syndrome and the Risk of Obstructive Sleep Apnea .................................................. 9
3.4 Craniofacial Anatomy ............................................. 9
3.5 Smoking and Alcohol Consumption ................................ 10
3.6 Familial and Genetic Predisposition .................................. 10

4 Obstructive Sleep Apnea Symptoms and Signs ............................. 11
4.1 Daytime Symptoms ................................................. 11
4.1.1 Excessive Sleepiness ............................................ 11
4.1.2 Excessive Sleepiness in the General Population and in Patients with Obstructive Sleep Apnea .............................. 12
4.1.3 Fatigue .......................................................... 14
4.2 Sleep-Related Symptoms .......................................... 15
4.2.1 Snoring, Witnessed Apneas and Nocturnal Choking ...... 15
4.2.2 Nocturia ....................................................... 16
4.3 Sequelae ............................................................ 17
4.3.1 Psychological Changes and Psychiatric Symptoms ............ 17
4.3.2 Health-Related Quality of Life ................................ 18
4.3.3 Performance Alterations ....................................... 19

5 Characteristic Clinical Features of Obstructive Sleep Apnea in Patients with Metabolic or Cardiovascular Disorders ................................. 22
Chapter 2

Inflammation, Oxidative Stress, and Procoagulant and Thrombotic Activity in Adults with Obstructive Sleep Apnea

1 Inflammatory Response to Chronic Intermittent Hypoxia
   1.1 Intermittent Hypoxia Activates Transcription Factors Involved in Inflammatory Processes
      1.1.1 The Nuclear Factor κB Pathway
      1.1.2 The Hypoxia-Inducible Factor Pathway
      1.1.3 Tissue-Specific Effects of Chronic Intermittent Hypoxia
   1.2 Oxidative and Nitrosative Stress
      1.2.1 Sources and Cellular Effects of Reactive Oxidative and Nitrosative Species
      1.2.2 Oxidative and Nitrosative Stress in Obstructive Sleep Apnea

2 Inflammatory Response to Sleep Loss and Fragmentation

3 Hypercoagulability and Thrombosis

4 Systemic Inflammation

5 Conclusions and Future Perspectives

6 References

Chapter 3

Metabolic Disorders Associated with Obstructive Sleep Apnea in Adults

1 Obesity and Obstructive Sleep Apnea
   1.1 Obesity Is the Major Risk Factor for Obstructive Sleep Apnea
      1.1.1 Definition of Obesity
      1.1.2 Clinical and Population Studies of the Relationship between Obesity and the Risk for Obstructive Sleep Apnea
      1.1.3 Impact of Treatment for Obesity on Obstructive Sleep Apnea Severity
      1.1.4 Gender Differences in Body Mass Index and the Risk for Obstructive Sleep Apnea
Contents

1.2 Visceral Obesity .................................................................74
1.2.1 Visceral Obesity May Affect the Anatomy of the Upper Airway ....75
1.2.2 Obesity and Upper Airway Collapsibility. ..............................75
1.3 Adipose Tissue, an Endocrine Organ ....................................81
1.3.1 Leptin ..............................................................................82
1.3.2 Adiponectin .................................................................84
1.3.3 Cytokines ........................................................................85
1.3.4 Other Adipokines ..........................................................86
1.3.5 In Summary .................................................................86
1.4 A Potentially Vicious Circle ..................................................86
1.5 Conclusion .........................................................................88
2 Alterations in Glucose Metabolism and Obstructive Sleep Apnea ........99
2.1 Assessment of the Regulation of Glucose Metabolism ...............99
2.1.1 Insulin Resistance ...........................................................99
2.1.2 Diabetes Mellitus ...........................................................99
2.2 Evidence for Alterations in Glucose Metabolism in Obstructive Sleep Apnea ........................................91
2.2.1 Clinical and Epidemiological Studies ..............................91
2.2.2 Therapeutic Studies .......................................................95
2.2.3 In Summary .................................................................99
2.3 Potential Mechanisms for the Development of Glucose Metabolism Alterations in Obstructive Sleep Apnea ..................................100
2.3.1 Inflammatory Dysfunction ...............................................100
2.3.2 Chronic Intermittent Hypoxia ...........................................102
2.3.3 Sleep Loss and Fragmentation ...........................................105
2.4 A Potentially Vicious Circle ................................................106
2.5 Conclusion .........................................................................109
3 Dyslipidemia and Obstructive Sleep Apnea ..................................114
3.1 Population and Clinical Studies of the Link between Obstructive Sleep Apnea and Dyslipidemia ..........................114
3.2 Effects of Continuous Positive Airway Pressure Administration on Dyslipidemia ...............................................117
3.3 Conclusion .........................................................................120
4 Metabolic Syndrome and Obstructive Sleep Apnea ......................123
4.1 Definition and Prevalence of Metabolic Syndrome ..................123
4.2 Obstructive Sleep Apnea and the Risk for Metabolic Syndrome .................................................................123
4.2.1 Prevalence of Metabolic Syndrome in Obstructive Sleep Apnea Patients ...............................................124
4.2.2 Effects of Obstructive Sleep Apnea on the Early Signs of Atherosclerosis in Metabolic Syndrome Patients .........124
4.2.3 Effects of Continuous Positive Airway Pressure Administration on Metabolic Syndrome ..............................124
4.3 Metabolic Syndrome and the Risk for Obstructive Sleep Apnea .................................................................124
4.4 Conclusion .........................................................................127
5 Liver Injury and Obstructive Sleep Apnea ......................................131
5.1 Characteristics of Nonalcoholic Fatty Liver Disease ................131
5.2 The ‘Two-Hit’ Theory ............................................................132

Liver Injury and Obstructive Sleep Apnea ..................................118
Metabolic Syndrome and Obstructive Sleep Apnea ........................118
Dyslipidemia and Obstructive Sleep Apnea ..................................110
A Potentially Vicious Circle ......................................................114
Conclusion ..............................................................................115

Visceral Obesity May Affect the Anatomy of the Upper Airway ....75
Obesity and Upper Airway Collapsibility. ..............................75
Adipose Tissue, an Endocrine Organ ....................................81
Leptin ..............................................................................82
Adiponectin .................................................................84
Cytokines ........................................................................85
Other Adipokines ..........................................................86
In Summary .................................................................86
A Potentially Vicious Circle ..................................................86
Conclusion .........................................................................88
Alterations in Glucose Metabolism and Obstructive Sleep Apnea ........99
Assessment of the Regulation of Glucose Metabolism ...............99
Insulin Resistance ...........................................................99
Diabetes Mellitus ...........................................................99
Evidence for Alterations in Glucose Metabolism in Obstructive Sleep Apnea ........................................91
Clinical and Epidemiological Studies ..............................91
Therapeutic Studies .......................................................95
In Summary .................................................................99
Potential Mechanisms for the Development of Glucose Metabolism Alterations in Obstructive Sleep Apnea ..................................100
Inflammatory Dysfunction ...............................................100
Chronic Intermittent Hypoxia ...........................................102
Sleep Loss and Fragmentation ...........................................105
A Potentially Vicious Circle ................................................106
Conclusion .........................................................................109
Dyslipidemia and Obstructive Sleep Apnea ..................................114
Population and Clinical Studies of the Link between Obstructive Sleep Apnea and Dyslipidemia ..........................114
Effects of Continuous Positive Airway Pressure Administration on Dyslipidemia ...............................................117
Conclusion .........................................................................120
Metabolic Syndrome and Obstructive Sleep Apnea ......................123
Definition and Prevalence of Metabolic Syndrome ..................123
Obstructive Sleep Apnea and the Risk for Metabolic Syndrome .................................................................123
Prevalence of Metabolic Syndrome in Obstructive Sleep Apnea Patients ...............................................124
Effects of Obstructive Sleep Apnea on the Early Signs of Atherosclerosis in Metabolic Syndrome Patients .........124
Effects of Continuous Positive Airway Pressure Administration on Metabolic Syndrome ..............................124
Metabolic Syndrome and the Risk for Obstructive Sleep Apnea .................................................................124
Conclusion .........................................................................127
Liver Injury and Obstructive Sleep Apnea ......................................131
Characteristics of Nonalcoholic Fatty Liver Disease ................131
The ‘Two-Hit’ Theory ............................................................132
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3</td>
<td>Obstructive Sleep Apnea and Liver Injury</td>
<td>119</td>
</tr>
<tr>
<td>5.3.1</td>
<td>Hepatic Enzyme Levels in Obstructive Sleep Apnea</td>
<td>119</td>
</tr>
<tr>
<td>5.3.2</td>
<td>Histopathological Evidence Linking Obstructive Sleep Apnea and Nonalcoholic Fatty Liver Disease</td>
<td>120</td>
</tr>
<tr>
<td>5.3.3</td>
<td>Is Liver Injury in Obstructive Sleep Apnea Consistent with the 'Two-Hit Theory'?</td>
<td>121</td>
</tr>
<tr>
<td>5.4</td>
<td>Conclusion</td>
<td>122</td>
</tr>
<tr>
<td>6</td>
<td>Conclusion and Future Perspectives</td>
<td>122</td>
</tr>
<tr>
<td>7</td>
<td>References</td>
<td>123</td>
</tr>
</tbody>
</table>

Chapter 4

**Endothelial Dysfunction in Adults with Obstructive Sleep Apnea**

1. Obstructive Sleep Apnea May Alter Vascular Structure
   1.1 Arterial Structure and Elastic Properties
   1.2 Cell Apoptosis and Endothelial Repair Capacity
2. Obstructive Sleep Apnea May Adversely Affect Endothelial Regulation of the Peripheral Vasomotor Tone
   2.1 Alterations in Nitric-Oxide-Dependent Vasodilator Mechanisms
   2.1.1 Vascular Reactivity
   2.1.2 Nitric Oxide Availability
   2.2 Alterations in Vasoconstriction Mechanisms
   2.2.1 Downregulation of Vascular Sympathoadrenergic Receptors
   2.2.2 Endothelin 1
   2.2.3 Angiotensin II
3. Potential Mechanisms Leading to Endothelial Dysfunction in Obstructive Sleep Apnea
   3.1 Chronic Intermittent Hypoxia/Reoxygenation
   3.2 Oxidative Stress
   3.3 Adipokines
   3.4 Hypercoagulability
   3.5 Sleep Loss and Fragmentation
   3.6 Confounders and the Development of Endothelial Dysfunction in Obstructive Sleep Apnea
4. Conclusion
5. References

Chapter 5

**Hemodynamic and Autonomic Changes in Adults with Obstructive Sleep Apnea**

1. Control of Cardiovascular Function during Normal Sleep Stages
2. Hemodynamic and Autonomic Changes during the Apnea-Ventilation Resumption Cycle
   2.1 Hemodynamic Changes
   2.1.1 Heart Rate and Blood Pressure
   2.1.2 Peripheral Resistance
   2.1.3 Stroke Volume and Cardiac Output
# Chapter 6

**Cardiovascular Disorders Associated with Obstructive Sleep Apnea**

1. **Limitations of Studies Found in the Literature** ................................................................. 199
2. **Obstructive Sleep Apnea and the Risk of Mortality from Cardiovascular Causes** ................. 200
   2.1 Clinical and Epidemiological Studies ................................................................. 200
   2.2 Day-Night Pattern of Death in Obstructive Sleep Apnea Patients ............................. 202
   2.3 Effect of Continuous Positive Airway Pressure Treatment on Mortality from Cardiovascular Causes ................................................................. 204
   2.4 Key Points ............................................................................................................. 206
3. **Systemic Hypertension** .............................................................................................. 206
   3.1 Clinical and Epidemiological Studies ................................................................. 206
   3.2 Blood Pressure Profile Abnormalities Associated with an Increased Risk of Obstructive Sleep Apnea ................................................................. 210
   3.3 Effects of Treatment for Obstructive Sleep Apnea on Blood Pressure ..................... 211
   3.3.1 Effect of Continuous Positive Airway Pressure Therapy ..................................... 211
   3.3.2 Effect of a Mandibular Advancement Device .................................................... 213
   3.4 Effects of Antihypertensive Drugs in Obstructive Sleep Apnea Patients .................. 214
   3.5 Mechanisms Potentially Involved in the Development of Sustained Hypertension in Obstructive Sleep Apnea ................................................................. 214
   3.6 Key Points ............................................................................................................. 215
4. **Heart Failure** ............................................................................................................ 215
   4.1 Obstructive Sleep Apnea Prevalence in Patients with Heart Failure ......................... 215
   4.2 Characteristic Clinical Features of Obstructive Sleep Apnea in Patients with Chronic Heart Failure ................................................................. 216
   4.3 Effects of Continuous Positive Airway Pressure Therapy ..................................... 218
   4.4 Mechanisms Potentially Involved in the Development of Heart Failure in Obstructive Sleep Apnea Patients ................................................................. 219
   4.4.1 Increased Blood Pressure and Other Cardiac Disorders ..................................... 219
   4.4.2 Chronic Intermittent Hypoxia ........................................................................... 220
   4.4.3 Sympathetic Overactivation ............................................................................. 221

**References** .................................................................................................................. 191
8.2 Ventricular Arrhythmias ......................................................... 246
  8.2.1 Clinical, Epidemiological and Therapeutic Studies .................. 246
  8.2.2 Key Points ................................................................. 247
8.3 Bradyarrhythmias ............................................................... 247
  8.3.1 Clinical, Epidemiological and Therapeutic Studies ................. 247
  8.3.2 Atrial Pacing and Treatment of Obstructive Sleep Apnea ........... 248
  8.3.3 Key Points ................................................................. 249

9 Conclusions and Future Directions ............................................ 249

10 References .................................................................................. 249

Subject Index .................................................................................. 267
Preface

The relationship between obstructive sleep apnea (OSA) and cardiovascular and metabolic diseases is a topical subject of concern to a wide range of specialists and general practitioners. In the last 2 decades, significant advances have been made in the understanding of factors contributing to, and the complications of, OSA. With the increase in the population levels of obesity (the greatest risk factor for OSA), the effects of OSA are likely to increase in the coming years; therefore, there is a corresponding need for wider education concerning this disease. The goal of this peer-reviewed book is, therefore, to provide a comprehensive and clear review of the current knowledge of the relationship between OSA and cardiovascular and metabolic diseases.

Separate chapters describe the definition, symptoms and sequelae of OSA in adults, and the diagnostic strategies and treatment options for adults with OSA according to the American Academy of Sleep Medicine (chapter 1). The pathogenic mechanisms by which OSA may contribute to the development and progression of cardiovascular and metabolic disorders, including inflammation, oxidative stress and thrombosis, are also explored (chapter 2). In addition, special emphasis has been given to the relationship between OSA and obesity, alterations in glucose metabolism, and metabolic syndrome and liver injury (chapter 3). The evidence for a relationship between OSA, endothelial dysfunction, autonomic dysfunction and cardiovascular disorders is also presented, and the results of studies investigating the effect of treatment for OSA on the concomitant cardiovascular disease are discussed (chapters 4–6). The chapters tend to emphasize human rather than basic animal data; nevertheless, animal data are cited, particularly, for example, with reference to the difficulties associated with unraveling the mechanisms of metabolic dysfunction in obese populations, in which the prevalence of comorbidities and potential confounding factors is high.

Each chapter summarizes the essential information and is illustrated by tables and figures, many of which are drawn from the articles cited in the text. It is my hope that these easy-to-read tables and figures will aid the readers in their understanding of the complex systemic interactions involved in this disease.

Alain Lurie, Paris
Acknowledgements

To Dr. Pierre Squara and the reviewers for their insightful comments and fruitful suggestions that have critically contributed towards the writing of this book.

To the sleep technicians Bérénice Guillaume Beulé, for her helpful assistance in editing the manuscript, and Theo Sokphon Teng and Caroline Lafif, for their assistance during the writing of this book.

To editor L.C. (www.editage.com) for his efforts in providing excellent-quality English editing assistance.