

Venous Thromboembolism in Bariatric Surgery

Eleni Zachari, Eleni Sioka, George Tzovaras and Dimitris Zacharoulis
*Department of Surgery, University Hospital of Larissa
Greece*

1. Introduction

Deep venous thrombosis (DVT) and pulmonary embolism (PE) constitute clinical presentations of the same vascular disease, known as venous thromboembolism (VTE). VTE is responsible for hospitalization of >250000 Americans annually. It is associated with high morbidity and mortality and represents a primary cause of preventable death. There is strong evidence that obesity is an independent risk factor for DVT and PE. Bariatric surgery is proven to be an effective means in the therapy of morbid obesity and its related comorbidities, thus its prevalence is rapidly increasing. Well established and widely performed procedures include laparoscopic adjustable gastric band (LAGB), Roux-en-Y gastric bypass (RYGBP), biliopancreatic diversion (BPD, with or without duodenal switch) and sleeve gastrectomy (SG). LAGB is a purely restrictive method, while RYGBP and BPD are considered as mainly malabsorptive procedures. SG was performed as a bridge to further by-pass surgery, however nowadays is performed as a single stage procedure. The risk of VTE in patients undergoing elective bariatric surgery is high, attributable to obesity, intraoperating factors and the lack of an established guidance describing optimal VTE prophylaxis. Overall incidence of VTE in this population is reported to be 1-3%. Diagnosis of PE postoperatively in obese patients can be difficult due to physical limitations and consequently may be underdiagnosed. Furthermore, although VTE is usually diagnosed as immediate postoperative complication, PE can occur in nonhospitalized patients, within the first month after surgery, despite pharmacologic prophylaxis.

2. Obesity

The most widely applied tool to diagnose obesity is body mass index (BMI). BMI is defined as weight in kilograms divided by the square of height in meters. World health Organization defines obesity as a $BMI \geq 30$. This cutoff was selected because according to epidemiological studies mortality curve increases at this value. Moreover, morbid obesity is defined as $BMI \geq 40$.

The prevalence of obesity increases rapidly in both developed and developing countries and is considered as one of the most serious public health problems.

Recent scientific data from long-term studies support the strong association between obesity and type 2 diabetes, hypertension, cardiovascular disease, dyslipidemia, arthritis, gallbladder disease, sleep apnea syndrome and many types of cancer. Furthermore, obesity deteriorates quality of life and induces severe psychological disorders.

3. Bariatric surgery

Bariatric surgery holds an important and well established role in the management of obese and morbid obese patients. Furthermore, it is proved to be the most efficient mode of treatment that provides sustained weight loss in morbidly obese patients.

International medical and surgical societies (International Federation for the Surgery of Obesity (IFSO), European Association for Study of Obesity (EASO), European Childhood Obesity Group (ECOG)) created guidelines in order to assure safe and effective clinical practice in the field of bariatric surgery.

3.1 Indications of bariatric surgery

- a. Patients from 18-60 years
 - with BMI ≥ 40 kg/m²
 - with BMI 35-40 kg/m² and with co-morbidity which weight loss is expected to improve (metabolic disorders, cardio-respiratory disease, severe joint disease, obesity-induced severe psychological problems)

To be candidates for surgical management, patients must have failed to lose weight or to maintain a substantial weight-loss following conservative treatment.

Bariatric surgery is indicated in patients who managed to lose weight prior to scheduled surgery and have reach a BMI below the required for surgery.

- b. Patients aged above 60

In these patients the primary objective is to improve quality of life. Benefits should be contemplated with potential risks, thus indications for surgery should be individualized.

3.2 Contraindications of bariatric surgery

- Absence of effort to lose weight following an appropriate non-surgical medical program.
- Psychotic disorders, severe depression, personality disorders.
- Alcohol abuse and/or drug dependencies.
- Life-threatening diseases (in a short term).
- Patients who are unable to care for themselves or to participate and conform to the required long-term medical follow-up.
- Patients in very high or unacceptable anaesthetic risk.

3.3 Bariatric surgery techniques

Nowadays a variety of surgical procedures is available for the surgical treatment of obesity. Furthermore, although primary objective of bariatric surgery is the weight loss, significant long-term amelioration or total remission of co-morbidities has been established. Bariatric surgery procedures modify the gastrointestinal track in order to reduce its volume and/or its absorptive function.

Restrictive procedures induce volume limitation and include laparoscopic adjustable gastric band (LAGB), vertical banded gastroplasty (VGB), laparoscopic sleeve gastrectomy (LSG), gastric bypass (GBP).

Malabsorptive procedures induce limited absorption of nutrients and include biliopancreatic diversion with (BPD-DS) or without duodenal switch (BPD).

Roux-en-Y gastric bypass (RYGBP), open or laparoscopic, encompasses characteristics of both types of procedures, as it provides restriction and mild- malabsorption.

4. Venous thromboembolism

4.1 Predisposing factors to venous thromboembolism in bariatric surgery

Morbid (BMI>50) and truncal obesity are identified as major predisposing factors for VTE. Sedentary lifestyle, increased abdominal pressure and excessive weight resting on the inferior vena cava drainage attribute to the increased risk. Additional risk factors include advanced age, history of previous VTE, immobilization, venous insufficiency and stasis, smoking, estrogen- containing oral contraceptives and hormone replacement therapy, hypercoagulable state, hypoventilation syndrome and anastomotic leakage. According to current literature, obesity interferes in intrinsic and extrinsic coagulation pathways, as well as in the anticoagulant mechanism, leading to a hypercoagulating state. Plasma concentration of fibrogen, von Willebrand, t-PA, PAI-1 and factor VII are significantly elevated in obese patients, while platelet aggregation is promoted due to leptin. There is evidence that treatment of morbid obesity can reverse partially some of the above abnormalities, as weight loss is associated with significant reduction in fibrogen, t-PA, PAI-1 and improvement of deficiency of antithrombin III.

Perioperative factors contributing to VTE include extend of surgical trauma, operative duration, length of postoperative immobilization and the use of general versus regional anesthesia. The risk of developing VTE depends on the type of major abdominal surgical procedure. Mukherjee et al. reported lower incidence of VTE among bariatric surgery patients (0.35%), while VTE rates were higher in patients undergoing nephrectomy, hepatectomy, colorectal resection, splenectomy, gastrectomy, pancreatectomy and esophagectomy. This lower rate may reflect strict adherence of bariatric surgeons to VTE prophylaxis guidelines relative to other surgical specialties.

More specifically, in laparoscopic bariatric surgery, reverse Trendelenburg position and pneumoperitoneum are associated with venous stasis of lower extremity and impaired venous return due to the compression of iliac veins and inferior vena cava. Furthermore several studies show the development of a hypercoagulable state during laparoscopy. Conversely, the risk of VTE during laparoscopy could be compensated by lower degree of surgical injury, early mobilization and reduced postoperative acute-phase response. Podnos et al. in a review of 3464 cases of GBP demonstrated that although the difference was not statistically significant, the incidence of PE was lower in laparoscopic group rather than the open group. In absence of randomized controlled studies, the evidence remains inconclusive as to the relative risk of VTE after laparoscopic bariatric surgery.

4.2 Prophylaxis of venous thromboembolism in bariatric surgery

4.2.1 Mechanical prophylaxis

Mechanical modalities include graduated compression stockings, intermittent pneumatic compression devices (IPC) and venous foot pump. Perioperative use of the above devices and early mobilization of patients reduce the risk of VTE by increasing venous outflow and preventing venous stasis. Remarkable advantage of mechanical prophylaxis is lack of interference in the coagulation path, which renders it safe for patients in high risk for bleeding. Limitations of the use of mechanical devices are skin irritation and poor compliance.

4.2.2 Pharmacological prophylaxis

Unfractionated heparin (UFH) and low molecular weight heparins (LMWH) are effective in the prophylaxis of VTE in surgical patients. An initial dose of 5000 units UFH is

administered subcutaneous preoperatively and repeated doses every 8 or 12 hours are required. On the contrary, LMWH shows improved pharmacological characteristics, as it requires a single dose per day, has lower degree of plasma protein binding, longer half-life and an enhanced bioavailability. Contraindications in anticoagulation agents are allergy, heparin-induced thrombocytopenia, coagulation disorders, active bleeding or patient at high risk of bleeding.

There is no consensus in literature considering the optimal regimen, dosage, and duration or application mode for VTE preventions in bariatric surgery patients. Furthermore, there is a paucity of data confirming the scaling of dosage according to body weight and renal function. Several authors support low rate of VTE when weight-adapted dosages are administered, while others suggest that there is no significant difference. American College of Chest Physicians recommend the administration of LMWH, UFH 3 times daily, fondaparinux or the combination of one of these pharmacologic method with optimally used IPC (Grade 1C). Although according to recommendations administered doses should be higher than those for nonobese patients (Grade 2C), adjusting doses according to BMI remain debatable. Current statement of American Society for Metabolic and Bariatric Surgery suggests the use of both mechanical and pharmacological prophylaxis in bariatric patients, without providing further adaptation guidance. Data on compliance of bariatric surgeons with the above guidelines are inconsistent, however treating high-risk bariatric patients seems to have a positive effect in adherence. Wu et al reported that 95% of bariatric surgeon comply with guidelines, while ENDORSE trial proved that only 58,5% of all surgical patients in risk for VTE receive prophylaxis.

4.2.3 The role of inferior vena cava filters

The prophylactic use of inferior vena cava filters (IVCF) remains controversial. Although recent studies report lower incidence of DVT and PE, other suggest that IVCF may reduce the rate of PE, but increase the incidence of DVT. Risk and complications deriving from the implantation of such a device should not be underestimated. Inferior Vena Cava, filter breakage, caval perforation, insertion site hematoma and infection have been reported. Based on the above, American Society of Hematology stated that the evidence to support the efficacy of IVCF in bariatric surgery is insufficient (Grade 2C recommendation against their use).

4.3 Diagnosis of venous thromboembolism

4.3.1 Clinical findings

Presenting symptoms of VTE are rather non-specific (dyspnea, chest pain, tachypnea), rendering the clinical diagnosis difficult. The key to early detection of VTE in bariatric patients is the high degree of vigilance for clinical features of DVT or PE. Physical examination may reveal increased respiratory rate, rales, wheeze, pleural friction rub, cyanosis, tachycardia, loud second heart sound, sings of DVT (oedema, redness, Homan's sign- pain on passive dorsiflexion of the ankle) and temperature above 38,5°C. Syncope and severe hypotension when present should be considered as signs of hemodynamic compromise.

In obese patients typical clinical findings of DVT or PE can be underestimated, as some of them (edema of lower extremity, tachycardia, dyspnea, tachypnea) pre-exist, due to obesity related co-morbidities, such as cardiac or respiratory failure, varicose veins, obesity related hypoventilation syndrome.

Clinical prediction rules were established in order to overcome the above limitations and provide effective risk stratification of VTE. Wells Score and Revised Geneva Score assess the clinical probability of VTE based on patient's risk factors and clinical findings.

4.3.2 Laboratory findings

The role of arterial blood gas (ABG) in the diagnosis of VTE is rather limited. Respiratory alkalosis and hypoxemia constitute common but non-specific findings and although their presence should raise suspicion, cannot be used solely for the confirmation of the diagnosis. D-dimers blood test detects a fibrin degradation product and has a high negative predictive value. In bariatric patients has limited value only to exclude VTE, as recent surgery, inflammation and trauma can induce false positive readings.

4.3.3 Imaging studies

Several diagnostic imaging studies can be performed in bariatric population, although limitations occur.

Electrocardiogram (ECG) in acute pulmonary embolism can reveal sinus tachycardia, ST segment depression and signs of right ventricular strain (more commonly incomplete right bundle branch block). Echocardiogram may detect right ventricular dysfunction. The high prevalence of cardiovascular diseases (coronary heart disease, left ventricular hypertrophy, atrial fibrillation, arrhythmias) in obese patients renders ECG and echocardiogram diagnostic tools of limited value.

Chest radiograph in acute pulmonary embolism may appear normal, while rarely, infiltrates, pleural effusion, atelectasis may be present. Consequently, chest radiograph is more useful in the exclusion of other pathological entities (pneumonia, pneumothorax) that may present with the same clinical picture with pulmonary embolism.

In the detection of DVT, Duplex Doppler Ultrasound remains the standard noninvasive examination for the visualization of thrombus, although when performed in obese patients may have reduced accuracy.

Chest Spiral CT has recently replaced pulmonary angiography and is now considered as the gold standard in the diagnosis of PE. However, special equipment must be available for morbidly obese patient, given the weight limitation of the conventional ones.

5. Differential diagnosis

Pathological entities that present with the same clinical features and signs as venous thromboembolism and should be part of the differential diagnosis are: pneumonia, pleural effusion, pneumothorax, congestive heart failure, and cardiac ischemia, exacerbation of chronic obstructive pulmonary disease, asthma and pulmonary edema.

Furthermore, differential diagnosis of PE after bariatric surgery should include anastomotic leakage, which may also present with tachycardia, fever, chest pain and respiratory insufficiency. An upper gastrointestinal study or surgical intervention may be necessary in order to exclude such a complication.

6. Treatment of venous thromboembolism

European Society of Cardiology guidelines and American Heart Association statement provide evidence-based therapeutic strategies of VTE. Hemodynamic and respiratory

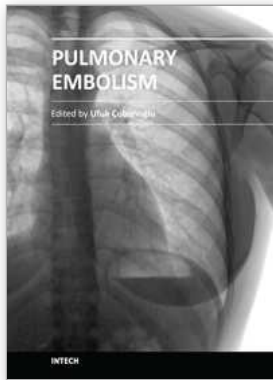
support is vital in patients presenting with PE and right ventricle dysfunction. Standard treatment remains the administration of UFH, LMWH and fondaparinux with the considerations mentioned in the prophylactic use of these agents. Data confirming the safety of weight-based dosage of LMWH are insufficient. Performance of thrombolysis, surgical pulmonary embolectomy, percutaneous catheter embolectomy and IVCF should be guided by evidence-based indications. In the absence of nationwide established guidelines standardized to this special surgical population, potential risk of all the above pharmacological and mechanical means should be taken into account when treating bariatric patients.

7. References

- Bonanomi G, Hamad GG, Bontempo F. Venous thrombosis and pulmonary embolism. In Schauer PR and Schirmer BD (Eds). *Minimally Invasive Bariatric Surgery* - Springer Verlag - New York 2007. Pp. 407-411
- Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004;292:1724.
- Clinical Issues Committee of the American Society for Metabolic and Bariatric Surgery. Prophylactic measures to reduce the risk of venous thromboembolism in bariatric surgery patients. *Surg Obes Relat Dis*. 2007 Sep-Oct;3(5):494-5.
- Cohen AT, Tapson VF, Bergmann JF et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008;371:387-394
- Eppsteiner RW, Shin JJ, Johnson J, van Dam RM. Mechanical compression versus subcutaneous heparin therapy in postoperative and posttrauma patients: a systematic review and meta-analysis. *World J Surg*. 2010 Jan;34(1):10-9.
- Fried M, Hainer V, Basdevant A, Buchwald H, Deitel M, Finer N, Greve JW, Horber F, Mathus-Vliegen E, Scopinaro N, Steffen R, Tsigos C, Weiner R, Widhalm K; Bariatric Scientific Collaborative Group Expert Panel. Interdisciplinary European guidelines for surgery for severe (morbid) obesity. *Obes Surg*. 2007 Feb;17(2):260-70
- Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *American College of Chest Physicians*. *Chest*. 2008 Jun;133(6 Suppl):381S-453S.
- Goldhaber SZ, Savage DD, Garrison RJ, et al. Risk factors for pulmonary embolism. The Framingham study. *Am J Med* 1983;74:1023-1028.
- Hamad CG, Choban PS. Enoxaparin for thromboprophylaxis in morbidly obese patients undergoing bariatric surgery; findings of the prophylaxis against VTE outcomes in bariatric surgery patients receiving enoxaparin (PROBE) study. *Obes Surg*. 2005;15:1368-1374.
- Hamad GG, Bergqvist D. Venous thromboembolism in bariatric surgery patients: an update of risk and prevention. *Surg Obes Relat Dis*. 2007;3(1):97-102.
- Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, Vedantham S, White RJ, Zierler BK; on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Peripheral Vascular Disease, and Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of

- Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association. *Circulation*. 2011 Mar 21.
- Kalfarentzos F, Stavropoulou F, Yarmenitis S, et al. Prophylaxis of venous thromboembolism using two different doses of lowmolecular- weight heparin (nadroparin) in bariatric surgery: a prospective randomized trial. *Obes Surg*. 2001;11:670-6.
- Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med* 2006;144:165-171.
- López-Jiménez F, Cortés-Bergoderi M. Update: systemic diseases and the cardiovascular system: obesity and the heart. *Rev Esp Cardiol*. 2011 Feb;64(2):140-9. Review
- Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis:surgical treatment of obesity. *Ann Intern Med*. 2005;142:547.
- Manganelli D, Palla A, Donnamaria V, Giuntini C. Clinical features of pulmonary embolism. Doubts and certainties. *Chest*. 1995 Jan;107(1 Suppl):25S-32S. Review.
- Mukherjee D, Lidor AO, Chu KM, Gearhart SL, Haut ER, Chang DC. Postoperative venous thromboembolism rates vary significantly after different types of major abdominal operations. *J Gastrointest Surg*. 2008 Nov;12(11):2015-22.
- Nguyen NT, Owings JT, Gosselin R, Pevac WC, Lee SJ, Goldman C, Wolfe BM. Systemic coagulation and fibrinolysis after laparoscopic and open gastric bypass. *Arch Surg*. 2001 Aug;136(8):909-16.
- Podnos YD, Jimenez JC, Wilson SE, Stevens CM, Nguyen NT. Complications after laparoscopic gastric bypass: a review of 3464 cases. *Arch Surg*. 2003 Sep;138(9):957-61
- Rajasekhar A, Crowther MA. ASH evidence-based guidelines: what is the role of inferior vena cava filters in the perioperative prevention of venous thromboembolism in bariatric surgery patients? *Hematology Am Soc Hematol Educ Program*. 2009:302-4. Review
- Rocha AT, de Vasconcellos AG, da Luz Neto ER, Araújo DM, Alves ES, Lopes AA. Risk of venous thromboembolism and efficacy of thromboprophylaxis in hospitalized obese medical patients and in obese patients undergoing bariatric surgery. *Obes Surg*. 2006 Dec;16(12):1645-55
- Roger VL et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation*. 2011 Feb 1;123(4):e18-e209.
- Sapala JA, Wood MH, Schuhknecht MP, et al. Fatal pulmonary embolism after bariatric operations for morbid obesity: a 24-year retrospective analysis. *Obes Surg*. 2004;14:738.
- Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. *Obes Surg*. 2002;12:19-24.
- Singh K, Podolsky ER, Um S, Saba S, Saeed I, Aggarwal L, Zaya M, Castellanos A. Evaluating the Safety and Efficacy of BMI-Based Preoperative Administration of Low-Molecular-Weight Heparin in Morbidly Obese Patients Undergoing Roux-en-Y Gastric Bypass Surgery. *Obes Surg*. 2011 Apr 9

- Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med.*2007;357:741-52.
- Stroh C, Birk D, Flade-Kuthe R, Frenken M, Herbig B, Höhne S, Köhler H, Lange V, Ludwig K, Matkowitz R, Meyer G, Pick P, Horbach T, Krause S, Schäfer L, Schlensak M, Shang E, Sonnenberg T, Susewind M, Voigt H, Weiner R, Wolff S, Wolf AM, Schmidt U, Meyer F, Lippert H, Manger T; Study Group Obesity Surgery. Evidence of thromboembolism prophylaxis in bariatric surgery-results of a quality assurance trial in bariatric surgery in Germany from 2005 to 2007 and review of the literature. *Obes Surg.* 2009 Jul;19(7):928-36.
- Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP; ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J.* 2008 Sep; 29(18):2276-315.
- Vaziri K, Bhanot P, Hungness ES, Morasch MD, Prystowsky JB, Nagle AP. Retrievable inferior vena cava filters in high-risk patients undergoing bariatric surgery. *Surg Endosc.* 2009 Oct;23(10):2203-7.
- Vaziri K, Devin Watson J, Harper AP, Lee J, Brody FJ, Sarin S, Ignacio EA, Chun A, Venbrux AC, Lin PP. Prophylactic Inferior Vena Cava Filters in High-Risk Bariatric Surgery. *Obes Surg.* 2010
- Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83:416-420.
- Wu EC, Barba CA. Current practices in the prophylaxis of venous thromboembolism in bariatric surgery. *Obes Surg* 2000;10:7-13.



Pulmonary Embolism

Edited by Dr. Ufuk Çobanoğlu

ISBN 978-953-51-0233-5

Hard cover, 236 pages

Publisher InTech

Published online 14, March, 2012

Published in print edition March, 2012

Pulmonary embolism is a serious, potentially life-threatening cardiopulmonary disease that occurs due to partial or total obstruction of the pulmonary arterial bed. Recently, new improvement occurred in the diagnosis and treatment of the disease. The aim of this disease is to re-review pulmonary embolism in the light of new developments. In this book, in addition to risk factors causing pulmonary embolus, a guide for systematic approaches to lead the risk stratification for decision making is also presented. In order to provide a maximum length of active life and continuation of functional abilities as the aim of new interventional gerontology, the risk factors causing pulmonary embolus in elderly individuals are evaluated, and the approach to prevention and treatment are defined. The risk of the development of deep vein thrombosis and pulmonary embolism, combined with obesity due to immobility, the disease of this era, irregular and excessive eating, and treatment management are highlighted. Non-thrombotic pulmonary emboli are also covered and an attempt is made to constitute an awareness of this picture that can change the treatment and prognosis of the disease to a considerable extent. In addition to the pathophysiological definition of pulmonary embolus, the priority goal of quick and definitive diagnosis is emphasized, and diagnostic strategies are discussed in the book. A numerical analysis of the vena cava filters, which is a current approach to prevent pulmonary emboli recurrences, is presented in the last chapter.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Eleni Zachari, Eleni Sioka, George Tzovaras and Dimitris Zacharoulis (2012). Venous Thromboembolism in Bariatric Surgery, Pulmonary Embolism, Dr. Ufuk Çobanoğlu (Ed.), ISBN: 978-953-51-0233-5, InTech, Available from: <http://www.intechopen.com/books/pulmonary-embolism/venous-thromboembolism-in-bariatric-surgery>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.