

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Ventricular Assist Device: Emerging Modality for Long Term Cardiac Support

Rachit Shah, Sharath Kommu,
Rohit Bhuriya and Rohit Arora

*Rosalind Franklin University/ Chicago Medical School
USA*

1. Introduction

More than 5 million people carry the diagnosis of heart failure in USA and almost 300,000 people die of heart failure each year in USA¹. Heart failure remains the most common discharge diagnosis for patients older than 65 years of age. In the Western world, most heart failure is related to coronary disease, and although the survival of patients post acute myocardial infarction has improved, this has resulted in an increase in the number of patients ultimately developing heart failure². Advances in medical therapy have resulted in improved survival in patients with moderate and severe heart failure, but the prognosis for end-stage heart failure patients remains poor³⁻⁵. In patients with end-stage heart failure cardiac transplantation remains the gold standard of cardiac replacement therapy and it has shown the greatest survival benefit. However, the supply of donor hearts is limited. There is also an increase in the number of heart failure patients who are not candidates for cardiac transplantation, mainly due to older age and presence of co-morbidities. There has therefore been considerable interest in alternative forms of cardiac replacement therapy, either as a temporary bridge to transplantation or as a definitive destination strategy. Multiple different mechanical devices for long-term circulatory support have been developed, ranging from total artificial hearts to ventricular assist devices (VADs). The main purpose of a VAD is to unload the failing heart and help maintain forward cardiac output and vital organ perfusion. Originally introduced as a temporary bridge to recovery and then as a bridge to transplantation, VADs have evolved into permanent or “destination” therapy for a growing number of patients with refractory heart failure⁶.

2. History and evolution of VADs

Mechanical circulatory support is rapidly emerging as an adjunct/alternative to cardiac transplantation. Its development commenced at the National Institutes of Health in 1964 in USA with the initial focus on development of a total artificial heart, but, with few exceptions, this has had limited success⁷. The major attention has now shifted to mechanical ventricular assist devices. The first successful cardiac-assist device in humans was implanted by DeBakey at the Texas Heart Institute in 1966⁸. Early devices were large and cumbersome with extracorporeal placement and provided temporary support only. The technological advancements led to the development of pulsatile LVAD design pioneered in

1976 as the Axio-symmetrical and Pierce-Donachy LVADs. A refined version of the latter device known as the Heartmate (Thoratec) was approved by the FDA as a bridging device to cardiac transplantation in 1994⁷⁸. Its updated version, the Heartmate XVE was approved as bridge therapy in 1998. The Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) study evaluated the long term benefit of Heartmate XVE placement compared with optimal medical therapy in end-stage heart failure patients⁴. There was 48% reduction in death from all causes, attributable to LVAD therapy compared with best medical therapy in this trial. On this basis, the Heartmate XVE was approved for use as destination therapy in 2002. With time VADs have evolved significantly, with three major changes to date: (a) Transition from pulsatile to continuous-flow devices; (b) Reduction in size with the preference for internal placement of the devices; (c) Use of electricity as a power source⁷⁹. The newest continuous-flow VADs are much smaller in size and are silent in operation, leading to significantly greater patient satisfaction⁷⁹. It makes this therapy more favourable for long-term support.

3. Components of a VAD

VADs support the failing heart by unloading the ventricle and generating flow to the systemic and/or pulmonary circulation. They can be used to support the left ventricle, right ventricle or both the ventricles. LVAD (Left Ventricular Assist Device) is the main assist device used in clinical practice. Use of isolated right ventricular assist device (RVAD) is a rare event⁸⁰. It is usually inserted around the time of placement of a (LVAD) to provide biventricular assistance. Sometimes biventricular mechanical ventricular assist devices are also used primarily for cardiac support. In comparison to single chamber VAD, biventricular mechanical devices create a complex system with two independent pumps, one right sided and the other left sided which supports both left and right ventricles.

VAD typically has an inflow cannula, an outflow cannula, a pumping chamber, per-cutaneous driveline, a controller and power supply. VADs are usually implanted through a median sternotomy, typically during cardiopulmonary bypass⁸⁰. The inflow cannula is connected to the heart and it decompresses the ventricular cavity and an outflow cannula returns blood to either the ascending aorta or the main pulmonary artery. The pumping chamber of the VAD is implanted sub-diaphragmatically to a pre-peritoneal or intra-abdominal position or may be situated in a para-corporeal position outside the body⁸⁰. Smaller devices are being developed for thoracic implantation, some with outflow to the descending aorta. A percutaneous driveline, containing the control and power wires, is tunnelled through the skin of the abdominal wall. It connects the device to an external portable driver consisting of an electronic or pneumatic controller and a power supply that may be worn around the waist, carried in a shoulder bag, or contained within a small bedside monitor.

Newer per-cutaneous VADs have a venous trans-septal inflow cannula that has a curved design at its end to facilitate ideal tip placement in the left atrium and contains a large end hole at its distal tip and 14 side holes to aspirate oxygenated blood from the left atrium. The cannula is attached to a continuous flow centrifugal blood pump, which in turn is driven by a 3-phase, brushless, direct current servomotor that is capable of delivering up to 5.0 L/min of blood flow. Blood is delivered from the pump to the femoral artery with an arterial perfusion catheter. This catheter ranges from 15F to 17F and pumps blood from the left atrium to the right femoral artery. Alternatively, two 12F arterial perfusion catheters pump blood into the right and left femoral arteries. The pump is driven by an external

microprocessor- based controller. A pressure transducer monitors the infusion pressure and identifies any disruption in the infusion line. An in-line air bubble detector monitors for the presence of air in the infusion line.

4. Types of VADs

Many VADs are currently available commercially or in various stages of development. These were developed to satisfy special needs for either short or longer-term support and, therefore, differ markedly in their design characteristics, principles of operation, hemodynamic capabilities, method of insertion, and, importantly, durability.

4.1 Percutaneous short-term devices

Percutaneous short-term VADs include devices that are inserted through the femoral artery and advanced to the left ventricle. Examples of such percutaneous short-term VADs are Impella 2.5 pump and TandemHeart. Impella 2.5 pump (Abiomed Inc., Danvers, MA) is an impeller-driven, axial flow pump, capable of pumping 2.5 L/min.¹³ TandemHeart (CardiacAssist, Inc., Pittsburgh, PA) is a low speed centrifugal continuous-flow pump that drains oxygenated blood through a catheter advanced across the interatrial septum to the left atrium and pumps it back to one or both femoral arteries.¹⁴ The experience with these devices is increasing, particularly with the Impella pump.^{15,16}

4.2 Longer-term assist devices

The currently available longer-term VADs are categorized into three generations, reflecting the order in which they were developed and the type of pumping mechanism they use.

4.3 First-generation VADs

These are pulsatile devices that use pusher plates and have inflow and outflow valves. These devices are efficacious at unloading the left ventricle and maintaining the circulation, with the capacity to pump up to 10 L/min⁷⁹. Examples of such devices are the HeartMate® I or XVE (Thoratec Corp., Pleasanton, CA) and the Novacor VAD (WorldHeart Inc., Oakland, California, USA)⁸¹. These implantable VADs are placed intra-abdominally or pre-peritoneally in a pocket under the abdominal rectus muscle and connected to the apex of the left ventricle and to the ascending aorta⁸¹. There is increased risk of hematomas and infections as they are large in volume, requiring extensive surgical dissection⁸¹. The percutaneous leads of these devices, especially those of the HeartMate XVE, are large and stiff and contain an air vent channel, which makes the system quite noisy and uncomfortable. All pulsatile devices have biological or mechanical valves to allow a unidirectional blood flow. Anticoagulation is necessary for all devices, except the HeartMate XVE. The latter has a textured inner surface of the pump stimulating formation of a biological layer preventing thrombus formation. Only aspirin is given as antithrombotic prophylaxis⁸¹.

Outcomes of first-generation devices

After the REMATCH study, Heartmate XVE was approved for use as “destination therapy” (DT) in 2002. Although the VAD therapy group had significantly greater survival and quality of life at both one and two years of follow-up, the survival at two years was only 28%. In addition, there were large numbers of readmissions and device-related

complications including sepsis and stroke. Therefore, use of Heartmate XVE as destination has not been widely accepted.

The first generation devices are also used successfully as a “bridge to transplantation” (BTT) with a perioperative mortality of 15–20% and an overall survival until device explantation of 60–70%⁸¹. However, in the majority of studies, the maximal support duration does not exceed 6 months, and in most studies mean support duration ranges only from 50 to 60 days.^{17–19} Results in experienced high volume centers (>10 implants per year) tend to be better than in low-volume centers. Survival and quality of life has been closely related to adverse events such as bleeding, infections, thrombo-embolic events and technical failures. Thrombo-embolic events resulting in transient ischemic attacks or even stroke is a devastating complication. In literature, there is a high variability in rates ranging from 5 to 50%, depending on the different LVAD types and variation in anticoagulation protocols⁸¹.

4.4 Second generation VADs

There is a need of more reliable and smaller devices due to growing waiting lists and long waiting times for heart transplantation. Second generation VADs can answer this need with smaller size and longer durability in comparison to first generation devices. The most common second generation VADs are the HeartMate 2 VAD (Thoratec Inc.), the Jarvik 2000 (Jarvik Heart Inc., New York, New York), Micromed DeBakey VAD and the Berlin Heart Incor (Berlin Heart AG). They have the continuous flow impeller pumps which are considerably smaller and safer to insert. Because they have only one moving part (the rotor), they are expected to be more durable than first-generation devices. To maintain an international normalized ratio (INR) of 2.0–2.5, the use of these pumps requires full anticoagulant therapy coupled with antiplatelet medications, such as aspirin or clopidogrel. The HeartMate 2 is the most successful second-generation device with over 2500 implants worldwide. It is one-seventh of the size and one-fourth the weight of the HeartMate XVE⁸¹.

Outcomes of second-generation devices

Heartmate II device has been approved by the US FDA for implantation as BTT in April 2008 and as DT in January 2010. The mean duration of support reported from the use of these continuous flow, rotary pumps is considerably longer compared with the first-generation devices (166–236 vs. 50–60 days). Two studies have shown 2 years survival of 65 and 69% with no mechanical failure and low fatal adverse event rates. The incidence of thrombo-embolic events in HeartMate 2 patients is in most studies comparable with those seen with Heart-Mate XVE, however the risk of hemorrhagic stroke rates tend to be higher (2–3%), probably as a result of the anticoagulation⁸¹.

4.5 Third generation VADs

Third-generation VADs are small centrifugal pumps in which the rotor is magnetically or mechanically suspended and, therefore, does not use ball bearings. Drivelines are less thick and more flexible. These features, coupled with the lower number of revolutions per minute, should enhance durability in comparison with the second generation pumps. Examples of such third generation VADs are the VentrAssist VAD (Ventracor Ltd, Chatswood, New South Wales, Australia)²⁰ and the DuraHeart (Terumo, Somerset, New Jersey, USA).²¹

Outcomes of third-generation devices

These devices are thought to last as long as 5–10 years, and their performance is being evaluated in several phase I studies involving the HVAD® (Heart- Ware, Miramar, FL)

devices, and more recently the DuraHeart® (Terumo Kabushiki Kaisha, Tokyo, Japan) system. They still carry the risk of neurological complications like stroke as well as risk of infections.

5. Clinical indications for VADs

Mechanical devices can be used for a wide spectrum of diseases based on the therapeutic goals of circulatory support as well as the duration of treatment. They can be used for short term as well long term duration. The indications are typically divided into 3 categories: bridge to recovery, bridge to transplantation, and destination therapy.

5.1 Bridge to recovery

VADs as a “Bridge to recovery” are used for patients who need only temporary support for days to weeks in anticipation of recovery of ventricular function followed by weaning and removal of device. This includes patients with acute inflammatory cardiomyopathies, acute cardiogenic or post-cardiotomy shock and myocardial infarction. The ability of LVADs to support an acutely failing heart while it recovers function is well documented.^{16,17,33} There are observations regarding the potential for myocardial recovery even in patients with chronic heart failure.

Various studies have documented that the unloaded left ventricle undergoes a process of reverse remodeling, as categorized by multiple different indices e.g. decrease in left ventricular size³⁴ and normalization of pressure-volume relationship curves.³⁵ Cellular structure and function also improves and reverts back toward normal.³⁶⁻³⁹ Thus, the reduction in left ventricular volumes is not just a function of the unloading provided by the VAD but actually reflects alterations in the dynamics of myocyte function.

5.2 Molecular changes in myocardium after VAD implantation

A reduction in myocardial contractility is one of the most important causes of dysfunction in heart failure.²⁵ Both the electrical and mechanical components of the process of excitation-contraction (E-C) coupling are altered, and Ca_2^+ handling is clearly a target for therapy in heart failure.²⁵ VAD therapy strongly affects E-C coupling. After VAD treatment, cardiomyocyte contractility is increased^{26,27} and the force-frequency relationship is normalized.^{28,29} Action-potential duration is reduced,^{30,31} mirroring the shortening of the QT interval on electrocardiogram in patients after prolonged support.³² In addition to E-C coupling mechanisms, several other molecular mechanisms responsible for VAD-induced reverse remodeling have been described. These include effects at the levels of metabolic pathways, immune and inflammatory responses, transcription factors, the adrenergic system, cytoskeletal proteins, the extracellular matrix, neurohormonal activation, and apoptosis and necrosis signaling, a breadth that suggests profound reverse remodeling at the molecular level. Clinically these changes improve left ventricular function and patients have a dramatic increase in their exercise capacity following LVAD implantation.⁴⁴⁻⁴⁶ These findings encouraged the explantation of LVADs in select patients who have demonstrated sufficient recovery of myocardial function. To date clinical results are mixed and although the large number of studies report regression or normalization of the pathological substrate following VAD treatment, the clinical evidence for recovery remains limited. To date, an average of only 5%–10% of patients who undergo mechanical circulatory support demonstrate adequate recovery of ventricular function to allow device explantation.^{33,34}

There is also concern that prolonged mechanical unloading reduces cardiac cell function, as well as cell size, in a time-dependent manner³⁵⁻⁴⁰ which may lead to myocardial atrophy. Unloading induced atrophy can be an important impediment to myocardial recovery and removal of the VADs for bridge-to-recovery, limiting the efficacy of VAD treatment.⁴¹ Minimizing unloading-induced atrophy may be an important strategy to obtain the beneficial effects of VADs and, to this end, a pharmacological regimen that includes clenbuterol has been tested in combination with VAD treatment. Clenbuterol is a unique β_2 adrenoceptor agonist that is currently approved only for patients with asthma, but has been shown in animal models to lead to significant hypertrophy of skeletal and cardiac muscle and enhanced mechanical strength of contraction.⁴² A novel combination regimen including the use of five oral medications known to provide various degrees of reverse remodeling, plus clenbuterol, was used in patients with non-ischemic cardiomyopathy who were transplant candidates and required a VAD for refractory heart failure.⁴³ In nearly 70% of patients on the combination therapy, the VAD could be removed within one year. After four years of follow-up, the average ejection fraction had improved from 15% preoperatively to 62%. These encouraging data have prompted the initiation of the Harefield Recovery Protocol Study (HARPS). The trial will not only assess clinical cardiac recovery but also explore molecular mechanisms of clenbuterol.

5.3 Bridge to transplantation

“Bridge-to-transplantation” is the strategy in which VADs are used for improving ventricular function and peripheral perfusion in patients awaiting cardiac transplantation. Several studies have demonstrated that VADs ensure sustained improvement in hemodynamic status and quality of life in patients awaiting cardiac transplantation.⁹ More than 80% of VAD-treated patients undergoing cardiac transplantation have a normal or improved post-transplant outcome.¹⁰

When implanted in patients refractory to medical therapy, LVADs lead to improved end organ function as well as overall physical conditioning.^{10,11} LVAD markedly decreases the filling pressures and increases cardiac output by taking over the work of the left ventricle, the. This leads to lower pulmonary vascular resistance and a reduction in afterload for the right ventricle. Additionally, the increase in cardiac output provides additional preload for the right ventricle, which further enhances its function. This improvement in right ventricular function and mechanical replacement of left ventricular output by LVAD results in more efficient delivery of oxygen to end-organ tissues. As a result, the presence of the LVAD can partially or totally reverse functional impairment of these organs. This is most clearly evident in the kidneys, in which renal failure can improve or resolve following the implantation of an LVAD. All organ systems benefit from the increase in perfusion, allowing sick patients to stabilize or improve as they wait for a heart transplant. In addition to providing an increased length of time on the organ waiting list, LVADs significantly improve outcomes by reducing patients' comorbidities at the time of transplant. This makes them better transplant candidates and improves their posttransplant outcomes.^{12,13}

The following criteria should generally be met prior to consideration of LVAD implant: clinical evidence of impaired end-organ perfusion with cardiac index <2 L/min/m², pulmonary capillary wedge pressure >20 mmHg, and systolic blood pressure <80 mmHg despite maximal medical support, including inotropes and an intraaortic balloon pump, if indicated.²⁰ Although it is important to meet these criteria, LVAD implantation should be performed before extensive end-organ damage for maximal chance of success.²¹

5.4 Destination therapy

“Destination Therapy” is perhaps the most exciting strategy in which VADs are used as an alternative to cardiac transplant to support the patients for their entire life. It involves the largest population of the patients with end stage heart failure who are unable to receive cardiac transplantation. The success of LVAD implantation as “Bridge to transplantation” (BTT) in candidates with refractory heart failure led to the investigations for its use as an alternative to Heart transplantation HT. The first DT feasibility trials were designed over 15 years ago. The REMATCH trial was one of the most remarkable endeavours in the history of VADs that assessed the feasibility of LADs for Destination Therapy (DT). The trial was conducted between May 1998 and July 2001 at 20 US hospitals. *REMATCH trial showed significant improvement of the quality of life in patients supported with LVAD and improved one-year survival from 25% to 52%.⁴ These data led to the US Food and Drug Administration (FDA) approval of the modified HeartMate XVE LVAD for use as DT in November 2002, thus launching a new era of surgical therapy for advanced heart failure.* One of the more recent trials the Heartmate II trial was conducted between March 2005 and May 2007 and it has shown that patients supported with HM II VAD (continuous flow VAD) had significantly improved two-year survival when compared to HM XVE recipients (58% vs. 24%, respectively) and significantly improved probability of freedom from stroke and device failure at two years, as compared to the recipients of pulsatile devices. These data led to approval of Heartmate II VAD for DT by US FDA in January 2010.

5.5 Indications for DT⁸²

The criteria for VAD implantation for DT are based largely on the entry criteria into the REMATCH trial. They are:

1. Class IV NYHA symptoms for at least 60 of the last 90 days despite maximized oral therapy, including dietary salt restriction, diuretics, digitalis, beta-blockers, and angiotensin converting enzyme (ACE) inhibitors (if tolerated), or requirement of inotropic support as outlined by the AHA/ACC guidelines for heart failure treatment
2. LVEF of $\leq 25\%$,
3. Peak oxygen consumption of < 12 mL/kg/min or documented inability to wean intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion
4. Contraindication to HT due to either age greater than 65 years or comorbidities such as insulin-dependent diabetes mellitus with end-organ damage, chronic renal failure, or others, and
5. Appropriate body size (≥ 1.5 m²) to support the HM XVE LVAD implantation.

5.6 Survival with DT

As mentioned earlier the results of the REMATCH trial revealed significant improvement in one-year survival from 25% to 52%.with improvement of the quality of life in patients supported with VAD in comparison with optimal medical therapy. In the post rematch era despite improvements in design, there was no significant improvement in clinical outcomes with pulsatile flow devices. Recently published Heart Mate II trial showed that patients supported with continuous flow HM II LVAD had significantly improved two-year survival when compared to pulsatile flow HM XVE recipients (58% vs. 24%, respectively) and significantly improved probability of freedom from stroke and device failure at two years, as compared to the recipients of pulsatile devices.

Experiences of the post-REMATCH era have shown that many DT recipients who were initially deemed not transplantable have improved their condition and became eligible for HT; 1 in every 5 recipients of HM XVE in the post-REMATCH era (17% of the 280 studied patients) underwent successful HT within 10 months from device implant. In most of these cases the improvements occurred due to the resolution of deemed irreversible pulmonary hypertension, recovery of renal function, weight loss, achieving cancer-free period, or reversal of other conditions. Therefore, one should not assume that DT would in the future preclude transplantation. Although LVAD implantation in the post-REMATCH era continues to be associated with substantial survival benefit as compared to medical therapy the outcomes of DT remain substantially inferior to those of HT (85% one-year survival).

6. Risk stratification and patient selection

Data from the REMATCH study⁴ and the more recent post-REMATCH Registry,⁸ of 300 recipients of the pulsatile HeartMate XVE device implanted as destination therapy since the close of REMATCH, as well as the HeartMate II trial²² with the continuous flow pump in patients awaiting heart transplant, have all demonstrated that nearly 70% of the deaths in the first year occurred prior to hospital discharge. This finding is clearly independent of the pump design or indication for its use and reflects the very high severity of illness of these patients at the time of device implantation.²³

The risk factors associated with death prior to hospital discharge were analyzed using data from the post-REMATCH Registry of destination therapy patients.²⁴ Those identified by multivariate analysis included platelets <149,000, prolonged coagulation (INR > 1.2), low pulmonary artery pressure (reflective of right ventricular failure), and importantly, malnutrition as evidenced by the crude marker of serum albumin <3.3 mg/dl. Hazard ratio was calculated for each of these preoperative laboratory variables, converted that hazard to a numerical score for each variable, and sum of these scores into a total risk score for in-hospital mortality was calculated. The data showed a tight linear correlation between higher risk score and increased in-hospital mortality, with high sensitivity and specificity. When the lowest-risk and medium risk cohorts were combined, the average survival was 70% at one year. For those with the highest risk score, the in-hospital mortality was >80% and a one-year survival was only 6%.

Many risk factors may be mitigated by intensive medical therapy; nutrition, coagulation profiles, right ventricular function, and renal function can be improved. Risk scoring can be used to select the optimal timing for device implantation. A patient with a very high or prohibitive risk score might undergo intensive medical management for a week, resulting in significant improvement in the risk score and a better outcome. These findings are based on the first generation of pulsatile pumps for destination therapy, but similar predictive accuracy has been recently reported in a large cohort of bridge-to-transplantation patients supported with both pulsatile and continuous-flow pumps.²⁴ If validated, the use of preoperative risk scoring will likely lead to improved outcomes with VADs.

7. Complications

Some of the most common perioperative complications of VAD placement include hemorrhage, right ventricular failure, sepsis, air embolism, and kinking of conduits. The late complications are mechanical device failure, neurologic events, and infection.^{4,44,45}

7.1 Mechanical failure

Mechanical failure of VADs is an important cause of morbidity and mortality in patients living with VADs, because of the prolonged support required for both bridge to transplantation and destination therapy. The REMATCH trial has shown that 35% of patients experienced component failure within 24 months of implantation.⁴ Another study on 109 patients with pulsatile VADs found that the probability of device failure was 6%, 12%, 27%, and 64% at 6 months, 1 year, 18 months, and 2 years, respectively.⁴⁶ On the other hand for continuous flow pumps the mechanical durability seems to be markedly improved. In one study on patients with a HeartMate II VAD as bridge to transplantation, only 5 of 133 (4%) developed either device thrombosis or a complication from surgical implantation necessitating device replacement.

Complications can arise in any component from the portable drive/system controller that controls and powers the device to the inflow and outflow cannulae, valves, batteries, and the VAD itself. These devices have system controllers and monitors that provide visual and auditory alarms during malfunction. To diagnose suspected device malfunction these alarms must be used in conjunction with clinical, laboratory, and imaging data. For troubleshooting, systematic catheter-, angiography-, fluoroscopy-, and echocardiography-based protocols have been developed to help diagnose common malfunctions.⁴⁷⁻⁵⁰ If necessary, repair of a dysfunctional VAD or removal and replacement with a new VAD may be performed.

7.2 Neurologic events

Implanted mechanical devices are susceptible to thrombo-embolic events due to their unique properties. The foreign surfaces of VADs can activate the immune system, platelets, and the coagulation cascade. In addition, the blood-contact surfaces of VADs along with turbulent blood flow increase the risk of shear stress on blood and thrombi formation.⁵¹ The unmasking or inadequate treatment of hypertension, older age, higher VAD flow and index, and inadequate anticoagulation further increase the risk for development of neurological events. Neurologic complications from VAD therapy include cerebro-vascular accidents and transient ischemic attacks, with an incidence ranging from 0.009 to 5.73 events per patient-year.^{51,52} The prevalence of neurologic events with destination therapy has ranged from 44% in the REMATCH trial (HeartMate XVE) to 57% in the European LionHeart Clinical Utility Baseline Study. Intracranial hemorrhage, syncope, seizure, brain abscesses, and encephalopathy have all been reported. These data are mostly from the bridge-to-transplantation experience and may not apply to destination therapy patients who are generally older and have more co-morbidities and longer implantation periods.⁵³

Not all devices have the same neurologic event rate. Design modifications like the use of novel biologic materials, textured coatings, and a single moving part, are believed to reduce the risk of thrombus formation. Promising data from the HeartMate II trial demonstrated reduced adverse events per patient year with respect to stroke (0.19 vs. 0.44) and non-stroke (0.26 vs. 0.67) neurologic events compared with a pulsatile flow pump⁸. Appropriate device selection, prevention of infection that can activate platelets, blood pressure control, and meticulous regulation of anticoagulation are all critical for the prevention of cerebro-vascular accidents after VAD implantation.^{54,55}

7.3 Infection

VAD infections occur most frequently between 2 weeks and 2 months after implantation⁵⁶. The predominant organisms are Gram-positive organisms *Staphylococcus epidermidis* and

Staphylococcus aureus followed by enterococci.⁵⁷⁻⁵⁹ Other commonly implicated organisms include Gram negative bacilli such as *Pseudomonas aeruginosa*, *Enterobacter*, and *Klebsiella* species, along with fungi.^{58,60} Frequent use of broad-spectrum antibiotics, particularly during the index hospitalization, is believed to increase susceptibility for fungal infections, which are associated with the highest risk of death.^{60,61}

The most common site of infection is the percutaneous driveline, which can often be managed successfully with wound care and antibiotics.⁶² However, a driveline infection can spread to other components of the VAD resulting in bacteremia, sepsis, and endocarditis⁶³. Sepsis in patients with mechanical assist devices has been reported to be the leading cause of death and can result in cerebral emboli and multi-organ failure.^{58,60} Other infections, including mediastinitis and peritonitis, have also been reported.

Many strategies have been adopted to try to minimize device-related and wound infections. Proper care of the driveline exit site must be maintained. Strict aseptic technique (e.g., sterile gloves, mask) must be followed when caring for the percutaneous exit site. The site should be gently cleaned with a mild antimicrobial soap and rinsed with sterile normal saline after which a dry sterile dressing should be applied. At all times, the driveline must be secured to minimize the risk of trauma; immobilization can be performed with an abdominal binder, additional gauze, tape, or a stoma-adhesive device.^{64,65} There are also many modifications made to device design to further decrease the risk of infection which include the use of larger single-lead drivelines and drivelines coated with chlorhexidine and silver sulfadiazine.^{60,66} Studies of rotary blood pumps with their reduced surface area for colonization and smaller surgical pump pocket suggest that they are less prone to infection.^{67,68}

8. Future directions

The combination of VADs with adjunctive therapies may result in further improvement in ventricular function and lead to higher rates of clinical recovery. VADs provides an ideal platform to apply adjunctive therapies that directly target the causes of disease and potentially lead to myocardial regeneration and full restoration of function.⁶⁹ An adjunctive therapy that is best evaluated in patients with mechanical circulatory support is stem cell therapy. The clinical trials of cell therapy performed so far using autologous adult progenitor cells in acute myocardial infarction patients⁷⁰ have shown limited efficacy, with little information on the mechanisms responsible for the small functional improvement observed.⁷¹ There is only less than 2% survival of transplanted cells in animals models present after two weeks post-transplant, and true cardiomyogenesis does not seem to occur.⁷² From this it appears that paracrine mechanisms are most likely to account for the improvements in functional recovery of the recipient myocardium.⁷³ Other cell types, such as embryonic stem cells, inducible pluripotent stem cells, and cardiac progenitor cells, have larger potential for cardiac regeneration but their integration in the recipient myocardium remains a crucial problem.⁷⁴ Cell delivery is usually given either by intracoronary or by peripheral intravenous injection, with only a few patients undergoing direct delivery into the wall of the cardiac ventricle.⁷⁵ Having the heart directly exposed at the time of the VAD implant as a bridge-to-transplantation allows the direct intracardiac injection of a large number of cells into very specific mapped areas of the ventricle and provides an opportunity to study the direct effects at the histological and molecular levels when the

heart is explanted for recovery or at time of transplant. In addition, the more favorable milieu offered by the VAD induced reverse remodeling, together with the reduced ventricular pressures, may promote the survival and integration of the injected cells, which would otherwise succumb in the hostile environment of the failing myocardium.

Gene therapy is also tried as an adjunctive therapy with VAD insertion, to manipulate critical genes differentially regulated in advanced heart failure^{76,77}. Gene transfer can be achieved either by using viral vectors or by transfection into the patient's progenitor/ stem cells to be used for cell therapy, prior to VAD surgery. Gene therapy could directly target mechanisms responsible for heart failure, aim to enhance angiogenesis or myogenesis and protect the transplanted cells from apoptosis, and prevent the unloading-induced negative remodeling.

9. Conclusion

Though cardiac transplantation remains the gold standard for cardiac replacement therapy, as donor hearts are a very limited resource, alternatives in the form of mechanical assist devices have become a useful solution in treating patients with end stage heart failure. The field of VAD therapy is clearly expanding, being used as bridge to transplantation and as destination therapy. The new generation of continuous-flow pumps has yielded encouraging preliminary data suggesting both improved outcomes and device durability. The development of validated risk stratification models will lead to improved patient selection and timing of device implant, with overall improved outcomes over time. The novel adjunctive therapies like the stem cell transplant and the gene therapy may well usher in a new era of enhanced utilization of these devices for truly sustainable ventricular recovery as an alternative to life-long support.

10. References

- [1] Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics, 2009 update. A report from the american heart association statistics committee and stroke statistics subcommittee. *Circulation* 2009;119:e21-181.
- [2] Miller LW, Missov ED. Epidemiology of heart failure. *Cardiol Clin* 2001;19:547-55.
- [3] Park SJ, Tector A, Piccioni W, et al. Left ventricular assist devices as destination therapy: a new look at survival. *J Thorac Cardiovasc Surg* 2005;129:9-17.
- [4] Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med* 2001;345:1435-43.
- [5] Hershberger RE, Nauman D, Walker TL, et al. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory end stage heart failure. *J Card Fail* 2003;9:180-7.
- [6] Fang J, Mensah GA, Croft JB, et al. Heart failure-related hospitalization in the U.S., 1979-2004. *J Am Coll Cardiol* 2008;52:428-34.
- [7] Nose Y. Implantable total artificial heart developed by Abiomed gets FDA approval for clinical trials. *Artif Organs* 2001;25:429.
- [8] Lietz K, Long JW, Kfoury AG, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. *Circulation* 2007;116:497-505.

- [9] Pagani FD, Miller LW, Russell SD, et al. 2009. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J. Am. Coll. Cardiol.* 54:312–21
- [10] Christiansen S, Klocke A, Autschbach R. 2008. Past, present, and future of long-term mechanical cardiac support in adults. *J. Card. Surg.* 23:664–76
- [11] Frazier OH, Benedict CR, Radovancevic B, et al. 1996. Improved left ventricular function after chronic left ventricular unloading. *Ann. Thorac. Surg.* 62:675–81
- [12] Aharon AS, Drinkwater DC Jr, Churchwell KB, et al. 2001. Extracorporeal membrane oxygenation in children after repair of congenital cardiac lesions. *Ann. Thorac. Surg.* 72:2095–101
- [13] Henriques JP, Remmelink M, Baan J Jr, et al. 2006. Safety and feasibility of elective high-risk percutaneous coronary intervention procedures with left ventricular support of the Impella Recover LP 2.5. *Am. J. Cardiol.* 97:990–92
- [14] Thiele H, Lauer B, Hambrecht R, et al. 2001. Reversal of cardiogenic shock by percutaneous left atrial-to-femoral arterial bypass assistance. *Circulation* 104:2917–22
- [15] Henriques JP, de Mol BA. 2008. New percutaneous mechanical left ventricular support for acute MI: the AMC MACH program. *Nat. Clin. Pract. Cardiovasc. Med.* 5:62–63
- [16] Mather PJ, Konstam MA. 2007. Newer mechanical devices in the management of acute heart failure. *Heart Fail. Rev.* 12:167–72
- [17] Frazier OH, Rose EA, Oz MC, Dembitsky W, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. *J Thoracic Cardiovasc Surg* 2001; 122:1186–1195.
- [18] Kalya AV, Tector AJ, Crouch JD, et al. Comparison of Novacor and HeartMate vented electric left ventricular assist devices in single institution. *J Heart Lung Transplant* 2005; 24:1973–1975.
- [19] El-Banayosy A, Arusoglu L, Kizner L, et al. Novacor left ventricular assist systems versus HeartMate vented electric left ventricular system as a long mechanical support device in bridging patients: a prospective study. *J Thoracic Cardiovasc Surg* 2000; 119:581–587.
- [20] Esmore D, Kaye D, Spratt P, et al. A prospective, multicenter trial of the VentrAssist left ventricular assist device for bridge to transplant, safety and efficacy. *J Heart Lung Transplant* 2008; 27:579–588.
- [21] Morshuis M, El-Banayosy A, Arusoglu L, et al. European experience of DuraHeart magnetically levitated centrifugal left ventricular assist system. *Eur J Cardiothorac Surg* 2009; 35:1020–1028
- [22] Miller LW, Pagani FD, Russell SD, et al. 2007. Use of a continuous-flow device in patients awaiting heart transplantation. *N. Engl. J. Med.* 357:885–96
- [23] Miller LW, Lietz K. 2006. Candidate selection for long-term left ventricular assist device therapy for refractory heart failure. *J. Heart Lung Transplant.* 25:756–64
- [24] Lietz K, Long JW, Kfoury AG, et al. 2007. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. *Circulation* 116:497–505
- [25] Kaye DM, Hoshijima M, Chien KR. 2008. Reversing advanced heart failure by targeting Ca^{2+} cycling. *Annu. Rev. Med.* 59:13–28

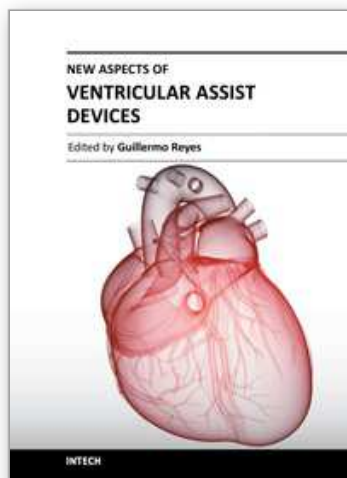
- [26] Terracciano CM, Harding SE, Adamson D, et al. 2003. Changes in sarcolemmal Ca entry and sarcoplasmic reticulum Ca content in ventricular myocytes from patients with end-stage heart failure following myocardial recovery after combined pharmacological and ventricular assist device therapy. *Eur. Heart J.* 24:1329–39
- [27] DiPaola K, Mattiello JA, Jeevanandam V, et al. 1998. Myocyte recovery after mechanical circulatory support in humans with end-stage heart failure. *Circulation* 97:2316–22
- [28] Heerdt PM, Holmes JW, Cai B, et al. 2000. Chronic unloading by left ventricular assist device reverses contractile dysfunction and alters gene expression in end-stage heart failure. *Circulation* 102:2713–19
- [29] Ogletree-Hughes ML, Stull LB, Sweet WE, et al. 2001. Mechanical unloading restores beta-adrenergic responsiveness and reverses receptor downregulation in the failing human heart. *Circulation* 104:881–86
- [30] Terracciano CM, Hardy J, Birks EJ, et al. 2004. Clinical recovery from end-stage heart failure using left ventricular assist device and pharmacological therapy correlates with increased sarcoplasmic reticulum calcium content but not with regression of cellular hypertrophy. *Circulation* 109:2263–65
- [31] Harding JD, Piacentino V III, Gaughan JP, et al. 2001. Electrophysiological alterations after mechanical circulatory support in patients with advanced cardiac failure. *Circulation* 104:1241–47
- [32] Xydas S, Rosen RS, Ng C, et al. 2006. Mechanical unloading leads to echocardiographic, electrocardiographic, neurohormonal, and histologic recovery. *J. Heart Lung Transplant.* 25:7–15
- [33] Maybaum S, Mancini D, Xydas S, et al. 2007. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. *Circulation* 115:2497–505
- [34] Mancini DM, Beniaminovitz A, Levin H, et al. 1998. Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure. *Circulation* 98:2383–89
- [35] Ritter M, Su Z, Xu S, et al. 2000. Cardiac unloading alters contractility and calcium homeostasis in ventricular myocytes. *J. Mol. Cell Cardiol.* 32:577–84
- [36] Kolar F, MacNaughton C, Papousek F, et al. 1995. Changes in calcium handling in atrophic heterotopically isografted rat hearts. *Basic Res. Cardiol.* 90:475–81
- [37] Welsh DC, DiPaola K, McNulty PH, et al. 2001. Preserved contractile function despite atrophic remodeling in unloaded rat hearts. *Am. J. Physiol. Heart Circ. Physiol.* 281:H1131–36
- [38] Oriyanhan W, Tsuneyoshi H, Nishina T, et al. 2007. Determination of optimal duration of mechanical unloading for failing hearts to achieve bridge to recovery in a rat heterotopic heart transplantation model. *J. Heart Lung Transplant.* 26:16–23
- [39] Ito K, Nakayama M, Hasan F, et al. 2003. Contractile reserve and calcium regulation are depressed in myocytes from chronically unloaded hearts. *Circulation* 107:1176–82
- [40] Soppa GK, Lee J, Stagg MA, et al. 2008. Prolonged mechanical unloading reduces myofilament sensitivity to calcium and sarcoplasmic reticulum calcium uptake leading to contractile dysfunction. *J. Heart Lung Transplant.* 27:882–89

- [41] Yacoub MH. 2001. A novel strategy to maximize the efficacy of left ventricular assist devices as a bridge to recovery. *Eur. Heart J.* 22:534–40
- [42] Soppa GK, Smolenski RT, Latif N, et al. 2005. Effects of chronic administration of clenbuterol on function and metabolism of adult rat cardiac muscle. *Am. J. Physiol. Heart Circ. Physiol.* 288:H1468–76
- [43] Birks EJ, Tansley PD, Hardy J, et al. 2006. Left ventricular assist device and drug therapy for the reversal of heart failure. *N. Engl. J. Med.* 355:1873–84
- [44] Gordon RJ, Quagliarello B, Lowy FD. Ventricular assist device-related infections. *Lancet Infect Dis* 2006;6:426–37.
- [45] Piccione W Jr. Left ventricular assist device implantation: short and long-term surgical complications. *J Heart Lung Transplant* 2000;19: S89–94.
- [46] Birks EJ, Tansley PD, Yacoub MH, et al. Incidence and clinical management of life-threatening left ventricular assist device failure. *J Heart Lung Transplant* 2004;23:964–9.
- [47] Horton SC, Khodaverdian R, Chatelain P, et al. Left ventricular assist device malfunction: an approach to diagnosis by echocardiography. *J Am Coll Cardiol* 2005;45:1435–40.
- [48] Catena E, Milazzo F, Montorsi E, et al. Left ventricular support by axial flow pump: the echocardiographic approach to device malfunction. *J Am Soc Echocardiogr* 2005;18:1422, e7–13.
- [49] Horton SC, Khodaverdian R, Powers A, et al. Left ventricular assist device malfunction: a systematic approach to diagnosis. *J Am Coll Cardiol* 2004;43:1574–83.
- [50] Scalia GM, McCarthy PM, Savage RM, Smedira NG, Thomas JD. Clinical utility of echocardiography in the management of implantable ventricular assist devices. *J Am Soc Echocardiogr* 2000;13:754–63.
- [51] Pae WE, Connell JM, Boehmer JP, et al. Neurologic events with a totally implantable left ventricular assist device: European LionHeart Clinical Utility Baseline Study (CUBS). *J Heart Lung Transplant* 2007;26:1–8.
- [52] Thomas CE, Jichici D, Petrucci R, Urrutia VC, Schwartzman RJ. Neurologic complications of the Novacor left ventricular assist device. *Ann Thorac Surg* 2001;72:1311–5.
- [53] Lazar RM, Shapiro PA, Jaski BE, et al. Neurological events during long-term mechanical circulatory support for heart failure: the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) experience. *Circulation* 2004;109:2423–7.
- [54] Tsukui H, Abela A, Teuteberg JJ, et al. Cerebrovascular accidents in patients with a ventricular assist device. *J Thorac Cardiovasc Surg* 2007;134:114–23.
- [55] Slaughter MS, Sobieski MA, Gallagher C, Dia M, Silver MA. Low incidence of neurologic events during long-term support with the HeartMate XVE left ventricular assist device. *Tex Heart Inst J* 2008;35:245–9.
- [56] Simon D, Fischer S, Grossman A, et al. Left ventricular assist device-related infection: treatment and outcome. *Clin Infect Dis* 2005;40:1108–15.
- [57] Kalya AV, Tector AJ, Crouch JD, et al. Comparison of Novacor and HeartMate vented electric left ventricular assist devices in a single institution. *J Heart Lung Transplant* 2005;24:1973–5.

- [58] Sivaratnam K, Duggan JM. Left ventricular assist device infections: three case reports and a review of the literature. *Asaio J* 2002;48:2-7.
- [59] Sinha P, Chen JM, Flannery M, Scully BE, Oz MC, Edwards NM. Infections during left ventricular assist device support do not affect posttransplant outcomes. *Circulation* 2000;102:III194 -9.
- [60] Gordon SM, Schmitt SK, Jacobs M, et al. Nosocomial bloodstream infections in patients with implantable left ventricular assist devices. *Ann Thorac Surg* 2001;72:725-30.
- [61] Nurozler F, Argenziano M, Oz MC, Naka Y. Fungal left ventricular assist device endocarditis. *Ann Thorac Surg* 2001;71:614-8.
- [62] Robbins RC, Kown MH, Portner PM, Oyer PE. The totally implantable Novacor left ventricular assist system. *Ann Thorac Surg* 2001;71: S162-5.
- [63] Holman WL, Park SJ, Long JW, et al. Infection in permanent circulatory support: experience from the REMATCH trial. *J Heart Lung Transplant* 2004;23:1359-65.
- [64] Chinn R, Dembitsky W, Eaton L, et al. Multicenter experience: prevention and management of left ventricular assist device infections. *Asaio J* 2005;51:461-70.
- [65] Pasque MK, Hanselman T, Shelton K, et al. Surgical management of Novacor drive-line exit site infections. *Ann Thorac Surg* 2002;74: 1267-8.
- [66] Zierer A, Melby SJ, Voeller RK, et al. Late-onset driveline infections: the Achilles' heel of prolonged left ventricular assist device support. *Ann Thorac Surg* 2007;84:515-20.
- [67] Siegenthaler MP, Martin J, Pernice K, et al. The Jarvik 2000 is associated with less infections than the HeartMate left ventricular assist device. *Eur J Cardiothorac Surg* 2003;23:748 -54.
- [68] Vitali E, Lanfranconi M, Ribera E, et al. Successful experience in bridging patients to heart transplantation with the MicroMed De- Bakey ventricular assist device. *Ann Thorac Surg* 2003;75:1200-4.
- [69] Renlund DG, Kfoury AG. 2006. When the failing, end-stage heart is not end-stage. *N. Engl. J. Med.* 355:1922-25
- [70] Abdel-Latif A, Bolli R, Tleyjeh IM, et al. 2007. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch. Intern. Med.* 167:989-97
- [71] Dimmeler S, Zeiher AM, Schneider MD. 2005. Unchain my heart: the scientific foundations of cardiac repair. *J. Clin. Invest.* 115:572-83
- [72] Murry CE, Soonpaa MH, Reinecke H, et al. 2004. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. *Nature* 428:664-68
- [73] Lee J, Stagg MA, Fukushima S, et al. 2009. Adult progenitor cell transplantation influences contractile performance and calcium handling of recipient cardiomyocytes. *Am. J. Physiol. Heart Circ. Physiol.* 296:H927-36
- [74] van Laake LW, Passier R, Doevendans PA, et al. 2008. Human embryonic stem cell-derived cardiomyocytes and cardiac repair in rodents. *Circ. Res.* 102:1008-10
- [75] Menasche P, Alfieri O, Janssens S, et al. 2008. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. *Circulation* 117:1189-200
- [76] Schneider MD, French BA. 1993. The advent of adenovirus. Gene therapy for cardiovascular disease. *Circulation* 88:1937-42

- [77] Murtuza B, Suzuki K, Bou-Gharios G, et al. 2004. Transplantation of skeletal myoblasts secreting an IL-1 inhibitor modulates adverse remodeling in infarcted murine myocardium. *Proc. Natl. Acad. Sci. USA* 101:4216-21
- [78] Barry A. Boilson, MB, MRCPI, MD, Eugenia Raichlin, MD, Soon J. Park, MD, and Sudhir S. Kushwaha, MD: Device Therapy and Cardiac Transplantation for End-Stage Heart Failure; *Curr Probl Cardiol*, January 2010
- [79] Cesare M. Terracciano, Leslie W. Miller, and Magdi H. Yacoub: Contemporary Use of Ventricular Assist Devices. *Annu. Rev. Med* 2010
- [80] Sean R. Wilson, MD, Michael M. Givertz, MD, Garrick C. Stewart, MD, Gilbert H. Mudge, JR, MD. Ventricular Assist Devices The Challenges of Outpatient Management; *Journal of American College of Cardiology* Vol 54, No 18, 2009.
- [81] J.R. Lahpor: State of the art: implantable ventricular assist devices; *Current Opinion in Organ Transplantation* 2009, 14:554-559.
- [82] Katherine Lietz, M.D., Ph.D. Destination Therapy: Patient Selection and Current Outcomes; *J Card Surg* 2010;25:462-471

IntechOpen



New Aspects of Ventricular Assist Devices

Edited by Dr. Guillermo Reyes

ISBN 978-953-307-676-8

Hard cover, 134 pages

Publisher InTech

Published online 29, August, 2011

Published in print edition August, 2011

Ventricular assist device has become one of the standard therapies for the support and the management of the failing heart. Updating our knowledge about these devices is mandatory in order to improve patient outcomes. In this book we can read the efforts made by many physicians concerned with the treatment of heart failure with mechanical devices. We all hope that the information compiled by experts in ventricle assist devices in this book will help us all to do better our main task - heal patients.

How to reference

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

Rachit Shah, Sharath Kommu, Rohit Bhuriya and Rohit Arora (2011). Ventricular Assist Device: Emerging Modality for Long Term Cardiac Support, New Aspects of Ventricular Assist Devices, Dr. Guillermo Reyes (Ed.), ISBN: 978-953-307-676-8, InTech, Available from: <http://www.intechopen.com/books/new-aspects-of-ventricular-assist-devices/ventricular-assist-device-emerging-modality-for-long-term-cardiac-support>

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
www.intechopen.com

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

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](https://creativecommons.org/licenses/by-nc-sa/3.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen