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Artificial organs

State-of-the-art technology for device-based and cell/tissue-based approaches

CONDENSED VERSION

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Foreword

This is a condensed version of the report ‘Artificial organs - State-of-the-art technology for device-based and cell/tissue-based approaches’. It aims to provide a summary of the state of the art with regard to the development of artificial organs. The complete report (RIVM report 360050011, 2008) can be found on the RIVM website (www.rivm.nl).

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Abstract

Artificial organs
State-of-the-art technology for device-based and cell/tissue-based approaches
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The challenge of treating diseased or failing human organs has been the driving force behind an increasing number of research programmes in recent years. Increased attention is being given to the potential of medical devices constructed from non-living materials as well as to applications utilizing living cells or tissues. Such products can serve as a bridge to transplant or serve as long-term chronic support systems. Artificial organs that can fully replace a failing organ are not yet commercially available.

This RIVM report provides a summary of the state of the art with regard to the development of both medical device-based and cell/tissue-based solutions for (partly) failing organ systems of the heart, lungs, liver, kidney, pancreas, bladder and bowel. These solutions are assessed for both total organ replacement and as technologies supporting or repairing damaged organs.

Established medical devices functioning as a bridge to transplant or as long-term chronic support systems currently exist for the heart, kidneys, pancreas and bladder. Clinical trials are ongoing with a total artificial heart device and with heart, liver and kidney support devices.

Cell/tissue products are not yet commercially available, although clinical trials in this field are ongoing for the heart and kidney. The results of research, including small-scale clinical trials, on the so-called bioartificial liver and pancreas, based on the use of porcine cells, were promising. However, the research on such bioartificial organs is currently banned in the Netherlands and many other countries for ethical and safety reasons.

Other applications for total artificial organs are not expected to enter clinical trials within the next 5 or even 10 years. Since Dutch academic research groups and clinicians are working on cutting-edge technology in this field, it can be expected that applications in Dutch clinics will closely follow international developments.

Key words:
artificial organs, medical devices, cell therapy, tissue engineering, regenerative medicine

Rapport in het kort

Artificiële organen
Stand der wetenschap voor benaderingen met medische hulpmiddelen en met cel/weefselproducten
VERKORTE VERSIE

Onderzoek naar oplossingen voor zieke of falende organen van de mens is de laatste jaren sterk in opkomst. Het gaat hierbij zowel om medische hulpmiddelen van niet-levende materialen als om toepassingen met levende cellen of weefsels. Dergelijke producten kunnen de wachttijd tot een transplantatie overbruggen, of de werking van een orgaan gedurende lange tijd ondersteunen. Kunstorganen die falende organen volledig kunnen vervangen zijn nog niet op de markt.

Dit RIVM-rapport geeft een samenvatting van de stand der wetenschap met betrekking tot de ontwikkeling van zowel medische hulpmiddelen als cel/weefselproducten die (gedeeltelijk) falende orgaansystemen ondersteunen, repareren of vervangen. Het gaat daarbij om het hart, de longen, de lever, de nieren, de pancreas, de blaas en de darmen.

Voor het hart, de nieren, de pancreas en de blaas bestaan medische hulpmiddelen als overbrugging naar een transplantatie of als langetermijnondersteuning van het orgaan. Er vinden klinische studies plaats met een totaal kunsthart, en met ondersteunende hulpmiddelen voor hart, lever en nieren.

Cel/weefselproducten zijn nog niet op de markt. Klinische studies vinden plaats voor het hart en de nieren. Onderzoek naar zogenoemde bioartificiële levers en pancreassen op basis van varkenscellen leek veelbelovend, ook in kleinschalig klinisch onderzoek. Vanwege ethische en veiligheidsredenen is dit momenteel in Nederland en vele andere landen verboden.

Andere concrete toepassingen voor totale kunstorganen worden de komende vijf tot tien jaar niet in klinische studies verwacht. Aangezien Nederlands onderzoek op dit gebied mondiaal vooraan meeloopt, zullen eventuele internationale doorbraken wel snel hun weg vinden in ons land.

Trefwoorden:
artificiële organen, medische hulpmiddelen, celtherapie, ‘tissue engineering’, regeneratieve geneeskunde

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Contents

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Introduction

Background

The early years of the 21st century show an acceleration of the introduction of innovative medical technologies. This revolution in the capabilities of medical technologies has been attributed to the coincidental emergence of several areas of science and technology which, when combined, will act as protagonists and strengthen each other. The most important areas involved are the biological sciences, nanotechnology, cognitive sciences, information technology and materials science. Many innovations are already resulting from the combination of these fields. Furthermore, new generations of medical technology products are being produced that increasingly cut across traditional demarcation boundaries such as medical devices, pharmaceutical products or human tissues. The trend to combine different technologies and the crossing of borders between traditional categories of medical products is commonly referred to with the term 'converging technologies'. An important category of products that is benefiting from such technological progress are the artificial organs. We use the following definition: *Artificial organs are products that are intended to be used for the (partly) support, replacement or regeneration of diseased, damaged or otherwise not fully functional organs.*

For patients with severely damaged organs, who are on a waiting list for a transplant organ, the availability of artificial organs could be the only way to survive. One way of creating artificial organs is the use of cell therapy and/or tissue engineering techniques. Also new medical device solutions based on mechanical, optical, (electro-)physical or other technological characteristics are being developed, as well as combination products using distinct features from both devices and cell products.
The Netherlands Health Care Inspectorate is aware that artificial organs are being developed at increasing speed. Since it is their role to keep a watching brief on the safe application of health care, they need to be prepared for the introduction of such new technologies. Therefore, they have commissioned the Dutch National Institute for Public Health and the Environment (RIVM) to provide an overview of the current state of affairs.

Aim

The aim of this condensed report is to provide a summary of the state of the art with regard to the development of artificial organs. A full report was published as RIVM report 360050011[1] in 2008. The full report also identifies universities, hospitals and commercial organisations working on such technology in the Netherlands.

Scope

The report describes both medical device-based and cell/tissue-based solutions for (partly) non-functional organs. This includes total replacement of an organ, as well as technologies to support or repair damaged organs. Organ transplantation is not included. The report is restricted to the following major organ systems: heart, lungs, liver, kidney, pancreas, bladder and bowel.

[1] The full report can be downloaded from: http://www.rivm.nl/bibliotheek/rapporten/360050011.html.

Methodology

This condensed report provides a summary of the state of the art with regard to the development of artificial organs. It was constructed by extracting information from a full report on this subject, which was published as RIVM report 360050011[2] in 2008. Updates on developments since the publication of the full report were not included in this condensed report. The full report was based on literature searches, internet searches, electronic newsletters and proceedings of conferences. Literature was identified from several sources including electronic data bases and cross-checking of reference lists. Electronic data bases consulted for scientific literature were Scopus™ (Elsevier BV) and Medline/PubMed (US National Library of Medicine). Internet searches were performed starting from the search engine Google (www.google.com). Product information was obtained using manufacturers' websites. Work in progress at universities, hospitals and companies was obtained from the relevant websites as well. In addition, interviews were held with key stakeholders in the Netherlands.

[2] The full report can be downloaded from: http://www.rivm.nl/bibliotheek/rapporten/360050011.html.

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Summary of the full report 360050011

Introduction

Artificial organs can be defined as products that are intended to be used for the (partly) support, replacement or regeneration of diseased, damaged or otherwise not fully functional organs. For patients with severely damaged organs, who are on a waiting list for a transplant organ, the availability of artificial organs could be the only way to survive. One way of creating artificial organs is the use of cell therapy and/or tissue-engineering techniques. Also medical device solutions based on mechanical, optical, electrical, physical or other technological characteristics can be applied, as well as combination products using distinct features from both devices and cell products. In recent years, important innovations have been realized in the field of medical technologies in general, which have also impacted the development of artificial organs.

This report provides a summary of the state-of-the-art with regard to the development of both medical device-based and cell/tissue-based solutions for (partly) failing organ systems of the heart, lungs, liver, kidney, pancreas, bladder and bowel. The report addresses total replacement of organs, as well as technologies to support or repair damaged organs, but not organ transplantations. Furthermore the report contains an overview of universities, hospitals and commercial organizations working on such technology in the Netherlands. The following paragraphs contain the developments for each organ in summary, followed by an overall conclusion.

Heart

Numerous devices have been developed for mechanical circulatory support in patients with end-stage heart failure. Ventricular assist devices (VADs) are in routine use as a bridge to transplantation, bridge to recovery, and long-term chronic support. The latest generation includes axial and centrifugal flow blood pumps. Also cardiac pacing and defibrillation devices are well established technologies. Currently, one total artificial heart (TAH, i.e. AbioCor™) is being used under the Humanitarian Device Exemption in the USA. The next generation TAH (i.e. AbioCor II) is being developed. It is smaller in size and therefore suitable for more patients. In Europe, the ACcor TAH and the MiniACcor TAH are currently being developed. These devices have been tested in animal studies and circulatory mock loops. In the Netherlands, chronic animal experiments with the MiniACcor are being planned at the Radboud University Nijmegen in cooperation with the Heart- and Diabetes Centre in Bad Oeynhausen (Germany) and the clinic for Thoracic- and Heart Surgery in Nijmegen.

Cell therapy of the heart seems to be the most abundantly practiced cell therapy in the clinic. Several approaches regarding cell source and cell delivery are being evaluated, of which the infusion and injection of bone marrow derived stem cells are the most abundant. This also accounts for the clinical studies that are performed in hospitals in the Netherlands. Many studies are ongoing and more are expected to be initiated in the future. In particular, a large multicentre trial in ten large Dutch hospitals is going on, as well as separate trials in Rotterdam and Leiden. In 2006, a clinical trial at the Medical Centre of Twente was cancelled by the Dutch Central Committee on Research Involving Human Subjects (CCMO) after 8 of 10 patients had been treated with injected stem cells. The trial had been initiated without approval of the CCMO. The manipulation of the stem cells before implantation was performed by the Dutch company Cells4Health BV (Leuvenheim, the Netherlands), a specialised company for the harvesting, treatment and storage of stem cells derived from both umbilical cord blood and bone marrow. Currently, the company is still offering a treatment of acute myocardial infarction called Health-Cardiac MI. This treatment is performed in collaboration with the University Hospital in Gaziantep in Turkey. As stated on the webpage of Cells4Health, the first patient (candidate for heart transplantation) has already been treated. This treatment is not acknowledged by the Dutch National

Health Service and is therefore not covered by the health insurers and can not be performed in the Netherlands.
Unfortunately, no major conclusions can yet be drawn based on the published studies conducted in the Netherlands. Based on the results obtained worldwide, feasibility and relative safety of cardiac cell therapy has been demonstrated. However, also large variation in efficacy is obtained, ranging from negligible to marginal. Although it can be considered that the proof-of-concept has been demonstrated, there is a need to explore and clarify the mechanism of action in order to improve efficacy. It can therefore be expected that many clinical studies as well as non-clinical studies will remain to be conducted in the coming years throughout the world, including the Netherlands.

Lungs
The natural lung represents a remarkable organ for gas exchange, and developing an artificial lung that approaches the gas exchange powers of the natural lung is a significant engineering challenge. Current hollow fiber blood oxygenators, as used in cardiopulmonary bypass, have membrane areas ranging from 1 to 4 m^2 that are packaged much less compactly than in the natural lung, with a surface area to blood volume ratio 10 times less than in the natural lung. The effective distance that gas diffuses between blood and gas flow pathways in artificial lungs is approximately 10–30 μm, an order of magnitude greater than in the natural lung. Thus, even with using 100% oxygen gas, artificial lungs currently used or under development aim at gas exchange levels that can only support resting metabolic needs in patients. None of the artificial lungs described in this report make an attempt to mimic any of the other functions or properties of the lung. The non-cell artificial lungs currently under development derive directly in a conceptual sense from the hollow fiber membrane and membrane module technology used in traditional clinical blood oxygenators.
Regarding the cell-based solutions, several approaches are being developed worldwide. These can be divided into the following categories: I) Targeted activation or administration of endogenous stem cells, II) Creation of pulmonary tissue constructs in vitro, III) Biohybrid lung that combines a medical device with living cells. All of these approaches are still in the research phase, although it has been reported that a cell-coated tracheal substitute has been applied in one patient (Germany). In the Netherlands the development of constructs with living cells to reconstruct, repair or replace pulmonary tissue and function has yet to be initiated. Therefore, it can be concluded that it is not expected that cell-based treatment of the lung will be applied in the Dutch clinics in the coming 5-10 years.
The challenge of biocompatibility inherent in making microvascular-scale blood channels with an extensive blood contact area, that is non-thrombogenic and non-inflammatory, may require the use of endothelial cells, perhaps genetically engineered for enhanced performance or for the robustness required in the application. Significant advances in tissue engineering, biomaterials, microfabrication, and bioengineering will all need to be harnessed for the technological development of future artificial lungs. Artificial lungs that allow patients any significant level of increased metabolic activity are not on the immediate horizon. At the same time, the need for artificial lungs in the distant future may be eclipsed by significant advances in regenerative medicine that enable tissue repair and regeneration of failing lungs.

Liver
Enthusiasm for liver support devices, particularly cell-based biological systems and albumin dialysis, has increased over the last decade resulting in considerable clinical activity both within and without the construct of clinical trials. Most data have been generated on patients with acute liver failure or on patients with decompensation of chronic liver disease, often referred to as acute-on-chronic liver failure. In clinical use for acute liver failure, bridging to liver transplantation is a more realistic goal rather than to transplant-free survival. In acute-on-chronic liver failure the objective of attaining clinical stability with treatment appears more achievable.

Currently, there is no single artificial organ or device capable of emulating all the functions of the liver. Some functions related to removal of toxic substances can be emulated by liver dialysis, charcoal hemoperfusion or plasma exchange, experimental treatments for liver failure. These methods have not yet been shown to improve the survival of patients with liver failure, although hemodialysis did work well on renal failure associated with liver failure. A small clinical trial (n=5) using a slow plasma exchange in combination with high-flow continuous hemodiafiltration showed some promise. The most promising medical device approaches at this moment are SPAD (single pass albumin dialysis) and MARS (molecular adsorbent recycling system), which combines conventional dialysis with albumin dialysis. Both approaches are still in an experimental phase and the future prospects rely on the performance of adequately powered randomized controlled trials. In the Netherlands artificial liver devices are currently not used on patients with acute or acute on chronic liver failure, although early stages of clinical studies on MARS therapy are being explored.
Medical device-based artificial liver support systems have a beneficial influence on the neurological state of patients, but do not improve survival. More beneficial effects have been expected from systems that bring the blood of the patient in contact with living liver cells, or: bioartificial liver systems (BAL). The cell activity can then contribute to the compensation of the failing patient liver, by e.g. detoxification, biosynthesis and biotransformation. The BAL may be developed as a bridge to transplant for patients suffering from acute-on-chronic liver failure or for some patients as a bridge to recovery.
The BAL based on porcine hepatocytes, is the most extensively evaluated type of biological device. A sizeable clinical trial failed to demonstrate efficacy, but secondary analyses suggest it would be unwise to assume that futility had been established with this device. Concern exists about the possible adverse immunological reactions towards the animal cells in the BAL, the transfer of cells into the patient which may lead to tumors and the transfer of retroviruses to the patient that may eventually pose a public health hazard. The further research of BAL devices incorporating porcine cells is banned in the Netherlands as well as in many other countries.

Kidneys

The kidney has multiple functions. Next to the excretion of waste substances, it also provides the overall important homeostasis of the blood through a sophisticated system of hormone excretion and re-absorption of minerals, water and proteins. Current hemodialysis therapy, which is the standard treatment for patients with end stage renal disease, does not provide the latter and, as a consequence, is associated with considerable morbidity and mortality. Two systems are under development that are expected to improve the renal replacement therapy and may lead to higher survival rates in patients that are waiting for kidney transplantation.
One system uses a pure medical device-based approach. It mimics the excretion and reabsorbtion function of the kidney by means of double filtration membranes. One membrane functions like a ‘classic’ hemofiltration unit. The second membrane is designed to reabsorb substances from the hemofiltrate, which are lost in the ‘classic’ hemodialysis. The selectivity of the membranes can be vastly improved by new production techniques. Smart nano-membranes can be designed to selectively pass molecules, not only based on the size of the molecules, but also on dielectric properties of the molecule.
A second possibility is formed by the use of living cells or tissues. The cell-based approaches that are currently in development can be divided into the following categories: I) Repair of the kidney by infusion of stem cells, II) Transplantation of fetal kidney tissue, III) Use of extracorporeal cell-coated devices, IV) Use of in vivo renal cell-coated matrixes. The most promising approach for the near future is likely to be the use of extracorporeal cell-coated devices, since this is the only approach that has entered clinical trials worldwide. This principle is based on a tissue-engineered bioartificial bioreactor that consists of a confluent layer of cultured proximal tubule cells seeded on the luminal side of

multiple polysulfone hollow-fibers. This bioreactor is combined with a conventional hemofilter and acts to mimic the process of tubular reabsorption. The results obtained in the clinical trials (USA) indicate that this approach is effective. In the Netherlands a similar approach is aimed to be developed as part of the BioMedical Materials Program (BMM). Although the ultimate goal is to develop an implantable bioartificial kidney, the first big milestone will be the creation of such an extracorporeal artificial bioreactor. Nevertheless, this program has just started and clinical studies in the Netherlands with cell-based artificial kidneys to repair, replace or reconstruct renal function are not expected in the coming 5-10 years.

Pancreas

A (bio-)artificial pancreas would improve the quality of life of insulin dependent patients and would have medical benefits. For over 40 years now, studies have been performed on the development of a closed-loop glucose measurement and insulin delivery system. In the last decennia progress has been made in the development of essential components: glucose monitors and insulin pumps. Both are commercially available, including dose advising algorithms and data management options, and the application possibilities become more sophisticated year after year. However, fully closed-loop systems are still not reliable and sufficiently accurate to be marketed. This is mainly due to problems with long term glucose measurement and to the complexity of dose controlling algorithms that have to respond to many different physiological circumstances. In the Netherlands, 15 patients are using a continuous glucose monitor in combination with an insulin pump. Furthermore, in 2007 a user evaluation study has started in 12 hospitals such a system in which the glucose monitor can communicate with the insulin pump. With these systems the patient still has to decide on the insulin dosing, based on the glucose levels displayed on the device.

Cell-based therapeutic options include the use of stem cells and the construction of a bio-artificial pancreas (BAP). Therapies for diabetes based on stem cells have yet not reached maturity and are still in the laboratory phase. BAPs can be intravascular or extravascular. The intravascular devices bear the risk of coagulation and thrombus formation and are currently not the approach of first choice. The extravascular devices do not present these problems and especially microcapsular devices have been studied extensively. Clinical investigations with BAPs are scarce, but have been carried out in the USA, Canada, Italy, Mexico and Russia. The latter two studies used porcine cells, which is not acceptable for ethical reasons in many countries including the Netherlands. To the best of our knowledge, clinical applications using a cell- or tissue-based artificial pancreas are currently not performed in the Netherlands.

Bladder

Several implantable medical device and (surgical) techniques are available for the treatment of bladder dysfunction. Some of these devices and techniques have proven to be successful, most notably sacral root stimulation, sacral nerve neuromodulation, and artificial urethral sphincters. Far-reaching surgical procedures (e.g., rhizotomy), technical failures (in case of artificial urethral sphincters), and the lack of selective neural activation must be overcome before these implantable medical devices can gain more widespread use. Many details regarding these techniques have yet to be elucidated. On the horizon are new and emerging technologies (e.g., BIONs, optical stimulation) that could contribute to accomplish improved bladder control. In the Netherlands, academic centres in Nijmegen, Utrecht, Rotterdam and Maastricht are involved in the clinical application of medical devices for the recovery of bladder function.

Several cell-based approaches for bladder repair, reconstruction and replacement are being explored worldwide. These approaches do not comprise the development of the bladder as a whole organ, but are focused on specific parts or diseases of the bladder: I) Recovery of the urethral sphincter, II) Treatment of vesicoureteral reflux, III) Recovery or replacement of the bladder wall. Clinical trials have been

performed or initiated in all of these groups, although to our knowledge none of these studies are currently performed in the Netherlands. Nevertheless, a European program in which the Netherlands is playing a key role and that most probably includes the development of a cell coated artificial bladder wall has been initiated in January 2007. Although it is difficult to predict, it cannot be excluded that early clinical trials using cell-coated artificial bladders will be initiated in the coming five years.

Bowel

Recent developments in sacral nerve stimulation, artificial bowel sphincter procedures, and dynamic graciloplasty are considered to be promising. Enthusiasm for any new technique often leads to overemphasis of the outcomes, and early reports are usually good. Outcomes can deteriorate with time and long-term results do not correspond to initial encouraging data such as for instance in case of the artificial bowel sphincter or dynamic graciloplasty. Both methods are technically demanding, with considerable morbidity, and substantial learning curve. Despite these obvious disadvantages, both artificial bowel sphincter and dynamic graciloplasty remain attractive to colorectal surgeons because once successful, they provide outstanding and long-lasting improvement of bowel function and quality of life. Unfortunately, these procedures require special equipment and their utility is limited because there is high morbidity to consider, which discourage coverage by health care insurers.
Tissue engineering approaches to create novel bowel tissue are currently still at the stage of proof-of-concept in small experimental animals. Promising research is going on for both small and large intestine. However, no clinical studies are expected in the near future.

Conclusion

In the field of artificial organs, many research programs are being performed on all major organ systems. However, only a limited number of the approaches have reached the phase of application in clinical use. Established organ support devices exist as a bridge to transplant or long-term chronical support for the heart, the pancreas and the bladder. Clinical trials are going on with a total artificial heart device, liver and kidney support devices and with cell therapy for the heart and a tissue-engineered bioreactor combined with dialysis functions to replace failing kidneys. The bioartificial liver and pancreas based on the use of porcine cells have shown some promise, also in previous small-scale clinical trials, but are currently banned in the Netherlands and many other countries for ethical reasons. For lungs, liver, kidneys, bladder and bowel both device-based and cell/tissue-based solutions are in various promising stages of development which are, however, not expected to enter clinical trials within the next 5 or even 10 years. Dutch academic research groups and clinicians are working at the front line in this field, implying that applications in Dutch clinics will closely follow international developments.

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Contents of the full report 360050011

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