1

Begeleidingsformulier aanvraag dierproef DEC- UM *Versie nov. 2005* **Herziene versie**	**DECNR: 2011-113** **Ontvangen: 31-08-2011**

DEC datum goedkeuring#	Type aanvraag [2]	**VROM/GGONR[3]**	**LNV/CBDNR[4]**
31-08-2011	Nieuw		

Hoofdproject	CARIM						
Deelproject	2						

Financieel beheerder		Budgetnummer	3098.2302 B

Titel van het onderzoek:

Leadless cardiac pacing using magnetic induction technology

startdatum 01-09-2011 einddatum 01-09-2014 *Duur van de proef[10]: 1 month*

	Naam	Tel (+ Tel privé enkel VO, VVO en VM)	E-mailadres	Bevoegd-heid[5]	Cap. groep /afdeling
1.Verantwoordelijk onderzoeker (VO)				Art.9	
2. Vervanger VO (VVO)				Art 12	
3. . overige uitvoerenden				Art. 9 Art 9	
4.				Art 12	

Diergroep	**1**	**2**	.	.	.	.	.
ctrl/exp/sham	acuut	chronisch					
Diersoort	43	43					
Stam							
Construct / mutatie ?	n	n					
Herkomst (leverancier) *	03	03					
Aantal	10	10					
Geslacht	v	v					
Dieren immuuncompetent ?	j	J					
Leeftijd/gewicht	40-70 kg	40-70 kg					
Doel van de proef *	12	12					
Belang van de proef *	1	1					
Toxicologisch onderzoek *	1	1					
Bijzondere technieken *	1	1					
Anesthesie *	4	4					
Pijnbestrijding *	4	4					
Mate ongerief *	2	4					
Toestand dier einde exp*	1	1					

2 Verantwoording

Aanvraag dierproef DEC-UM

Titel: **Leadless cardiac pacing using magnetic induction technology**

1. Doel van de proef.
Although pacemaker therapy is more than 50 years old, this therapy still has several problems. Of the total pacing systems the leads (electrode-wires) are the Achilles heel of the system. Within ten years after the implantation of the pacemaker 21% of the patients with cardiac pacing encounter lead failure. Moreover, some desired locations for the pacing lead are hard to reach with wired leads. Therefore, pacing the heart without leads (using wireless electrodes) in a position, not predetermined by a given coronary sinus anatomy would ameliorate pacing options essentially. Therefore, the aim of this study is to test the limits and efficiency of a leadless pacing system, based upon novel magnetic induction technology.

2. Maatschappelijke relevantie en/of wetenschappelijk belang
In the USA each year about 400,000 pacemakers are implanted. Although pacemaker therapies are more than 50 years old, the therapy still suffers from some practical problems. The clinical complications associated with pacemakers can be primarily attributed to the pacemaker leads. Arnsbo et al. demonstrated that 21% of the patients with cardiac pacing encounter lead failure within ten years after the implantation of the pacemaker. This lead failure may be due to fracture of the lead (leaky isolation) as well as infection in the pacemaker pocket spreading towards the heart along the leads. Further complications may occur due to the leads implanted in the coronary sinus (for biventricular pacing therapy for heart failure), including stimulation of the phrenic nerve. Finally, in all pacemaker therapies the position of the lead determines the hemodynamic outcome (cardiac pump function). Such optimal positions are often difficult to reach with wired-leads. Therefore, it is to be expected that leadless (or: wireless) pacing may offer several advantages over the conventional way of pacing. Recently, demonstrated the capability of using endocardial pacing of the heart via magnetic induction technology in a single animal experiment (1). This magnetic induction technology was chosen as energy transmission because of its low energy demand. The latter may be a considerable advantage over the transmission using ultrasound, as used in the only other concept of wireless pacing (2). A further advantage as compared to ultra-sound technology may be the lower sensitivity to poor conduction of the signal by ribs and lungs.

3. Alternatieven
This project investigates the capability of leadless pacing. **The fact that we need to know the best way to stimulate the heart using coils applied under the skin makes that we need intact animals; the fact that the technique will be used in humans makes that we need animals with a body size in the same order of magnitude as men.** Therefore, in vitro studies or other alternatives are not an option.

4. Ethische afweging
This study is very important to test the potential of a breakthrough technology that would allow for resolution of the following problems in a large population of patients:
1) lead related issues (e.g. break, infection) and related burden (obviate need for repair, re-operation)
2) Improve pacing therapy efficacy e.g. improve cardiac resynchronization efficacy by providing left ventricular endocardial pacing

Therefore, we think that it is ethical to subject the animals in this study to the mild to moderate discomfort.

5. Wetenschappelijke onderbouwing

Despite tremendous technical advancements during the last decades, pacemaker therapy is still associated with a considerable rate of complications. In this context, the leads of the pacemaker seem to present the Achilles' heel of the system. Lead failure occurs in about 21% within 10 years after pacemaker implantation (3,4). Besides these complications, venous leads cannot be applied on children due to the risk of venous thrombosis and to the expected growth. In addition to these technique-related complications, the transvenous lead placement in current pacemaker technology is associated with hemodynamic disadvantages due to right ventricular pacing (5). If resynchronization is necessary, left-sided stimulation can only be achieved by positioning the lead in the coronary sinus. However, due to an unfavorable anatomy of up to 30% of the patients, a suitable target vessel cannot be reached and many suffer from phrenic nerve stimulation (6). Moreover, leadless pacing enables to position the left ventricular pacing lead at the endocardium of the left ventricle, which is a position that results in better hemodynamic effects of CRT (7).

Therefore, a leadless pacing system could considerably improve pacemaker therapies.

The stimulation system, developed by (1), consists basically of two components: (a) a transmitter unit (primary coil) implanted under the skin or the major pectoral muscle just above the heart and (b) a small receiver unit (secondary coil) implanted in the right or left chamber of the heart. The energy for the

voltage pulse to stimulate the heart is transmitted by the magnetic field. Thereby, the subcutaneous coil generates an alternating magnetic field and the receiver coil in the heart converts this energy into voltage pulses for stimulation.

By applying the concept of direct conversion, the desired shape of the pulse is obtained by the specific properties of the receiver coil (shape, number of turns, appropriate core material, capacitor, rectifier) and by the characteristics of the external magnetic field. Consequently, the stimulation pulse characteristics (amplitude and duration) can be freely modified by programming the transmitter unit comparable to conventional pacemaker systems.

The preliminary feasibility study (1) showed that endocardial pacing of the heart was feasible and could be maintained during an acute experiment. However, for further development of a system that can be employed in patients, more information is required about how to design the system. Important issues are the anatomical and electrical coupling between emitting coil and receiver, impact of receiver orientation, chronic maintenance of therapy and optimal shape of the pacing stimulus.

6. Wetenschappelijke beoordeling

This protocol has been read and approved by I

7. Proefdier keuze

7a. Soort, stam / herkomst / eindbestemming

Goats 40 -70 kg. Goats we will be acquired by CPV from local farms. We have extensive experience with chronic pacing and measurements in awake goats. In the second study we would like to test the efficacy of chronic leadless pacing

7b. Sexe

Female goats. Housing of male goats causes considerate nuisance concerning malodour.

7.c. Aantallen

In this study we are not aiming at statistical significances, therefore no power calculation can be made. The endpoints for the studies in the acute study are ability to pace adequately (for short (acute study) and long term (chronic study). Reproducibility of the procedure has to be assessed, for which we consider 6 complete sets of successful experiments sufficient. For both protocols we think that we need 4 additional experiments due to technical development that may be needed while testing this novel technology. Therefore, we ask for 10 animals in both protocols. Importantly, in the acute protocol the first experiments will be evaluated one by one, in order to improve the next experiment. Furthermore, the chronic experiments will only be performed if the acute studies were successful and the position of the coils used in the chronic studies will be derived from the acute studies.

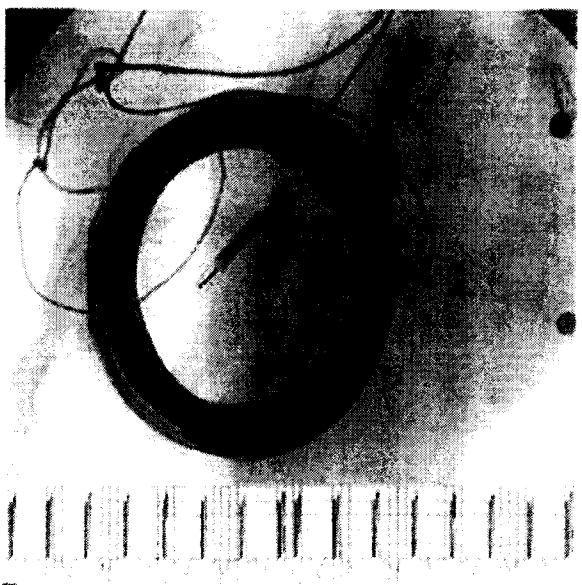

Figure: Arrangement of transmitter and receiver coils during leadless pacing. Receiver unit without external connection in the right ventricle, as used in the proof-of-principle experiment (1). The transmitter unit is placed on the outer thoracic wall directly beyond the receiver unit. Bottom: ECG tracing during wireless pacing.

8. Experiment

Acute study

Protocol 1: Acute studies:

Aim: test the coupling of receiver-emitter for different receiver and emitter positions/orientations

Animals will be implanted with:

- 4-6 emitting coils (6 cm flat doughnut, soft), placed subcutaneously on the right and left chest
- a receiver, attached to a steerable catheter, that will be introduced in the carotid artery (access to left side of the heart) and/or jugular vein (right side of heart) navigated within the chambers of the heart i.e. Right Ventricle, Right Atrium, Left Ventricle.

Position of the emitter coils with respect to the heart and to the sensing coil will be determined using the EnSite™ Navix system. The coils sense the electrical signals transmitted between three pairs of EnSite Navix electrode patches attached to the chest of the animal. The EnSite™ System collects these data and uses this information to track or navigate their position and movement and construct three-dimensional (3-D) models of the chest and cardiac chamber. Additional anatomical information will be acquired using X-ray imaging in two directions.

Collected signal (emitted by emitter), pacing threshold and characteristics will be measured for selected positions and stimulation algorithms. Energy efficacy will be calculated.

At the most optimal location, the receiver will be attached to endocardium and truly leadless pacing will be administered and capture monitored (overpacing) for 10-30 min.

Endpoints of the study are the ability to pace the heart and pacing thresholds.

Chronic study

Protocol 2: This study will be conducted (only) after successful accomplishment of the acute studies, using the best settings obtained in the acute study.

Aim: Testing whether the leadless pacing system is able to perform ventricular pacing for the duration of 1 month.

Animals will be instrumented similar to protocol 1, except that only two emitter coils will be positioned subcutaneously (at sites that proved to be best in protocol 1) and that one or two truly leadless receiver will be implanted in the right ventricle.

After site selection of receiver and emitter pair, the emitter coils will be connected to electronics placed in a small bag secured on animal back.

In order to mimic the application of pacing in the clinic and to enable optimal monitoring of the continuity of pacing, atrioventricular block will be induced in these goats, using RF-ablation. As back-up, a conventional pacemaker with lead in the right ventricle is implanted.

Administration of therapy will be monitored using subcutaneously implanted ECG electrodes connected to a recording system, using a transdermal cable. In addition, the memory of the conventional pacemaker can be read out for the percentage of all heart beats that this pacemaker has been pacing.

9. Experimentele condities

9a. Anesthesie

An employee of CPV shall perform an extensive pre-anesthetic examination .

before the surgery, animals fast for 12 hours (no food, hay; housing on straw; water *ad libitum*).

Induction:

Thiopentalnatrium 10-20 mg/kg i.v.

9. Expe

Acute st

Chronic

9a. Ane

Maintenance of anesthesia: total anesthesia using Sufentanyl (6 µg/kg/h), Midazolam (0,8mg/kg/h), Propofol (10mg/kg/h) en Pavulon (0,3mg/kg/h); ventilation using air/O_2 (2:1). compensation of fluid loss using ringers lactate 500 ml/u i.v.
Monitoring:
During anesthesia monitoring is performed from the ECG en spirometry. In case of use of muscle relaxants (Pavulon) also blood pressure will be monitored. This degree of monitoring provides sufficient information for detecting a possibly masked pain response.

9b. Pijnbestrijding
Sufentanyl provides perioperative analgesia. for the animals in the acute study analgesia during anesthesia is sufficient.
Recovery from anesthesia (Chronic study): day 1 Buprenorfine 5-10 µg/kg i.m. 2 /day i.c.m. Caprofen 2-4 mg/kg s.c. Day 2 en 3 enkel Caprofen 2-4 mg/kg s.c. Beside analgesics also 3 to 5 days postoperatively antibiotics will be given.
Pain and health will be evaulated using clinical parameters, like heart rate, respiratory rate and pattern, behavior and skin appearance.

9c. Euthanasie en Humane eindpunten

- Euthanasia will occur during full anesthesia, as described above. The chest is opened at the left side, the heart is removed, so that the goat bleeds to death

Humane eindpunten (alleen relevant voor de chronische studie):

- In case of uncontrollable infections, despite treatment with antibiotics. Infections are identified by a body temperature above 40^0 C.
- In case of heavy pain despite adequate analgesia. Pain is identified by a irregular skin/coat, hanging of the head and grinding of teeth,
- In case of weight loss $\geq$ 20 % compared to the pre-anesthetic examination. In increase in weight caused by edema is not expected in these animals, because they are not expected to develop heart failure

9b. Pijn

9c. Eutl
animals
system

Zorg

10a. Ongerief

Intervention	Duration	Frequency	Discomfort score
Induction anesthesia	5 min	1	02
Total			**02**

Intervention	Duration	Frequency	Discomfort score
Induction anesthesia	5 min	1	02
Anesthesia and recovery	4 hours	1	03
Subcutaneous coil implantation	1 month	1	03
Chronic pacing	1 month	1	02
Solitary housing	1 month	1	03
Total			**04**

10b. Welzijnsevaluatie

The group has extensive experience with implantation of pacing systems, so this is not expected to create major problems. An issue requiring more attention is the "porte-d'entrée" created by the two cables that cross the skin of the animals. However, our group has extensive experience with this approach. In the past technical improvements have been made, so that even during 4 months-experiments very few infections occur.

11. Verzorging en huisvesting

Goats will be housed at the inner stables of CPV. Because the goats in the chronic study will carry recording equipment, group housing is impossible. Goats are very eager to chew materials, which are present in their cages. The goats will be able to see each other.

12. Deskundigheid

Personnel have many years of experience in working with large laboratory animals and these types of procedures.

13. Standard Operation Procedures (SOP)

Acute measurements: insert catheter into jugular vein using 8F introducer and move it towards the right atrium and right ventricle, in closed chest situation. Insert emitter coils subcutaneously at six positions (3 right, 3 left, varying in rostro-caudal position. Skin is closed over the coils.

Chronic experiments: Implanting 2 emitting coils subcutaneously and close skin.
Pacing coil is implanted in the RV apex using a catheter that releases the leadless coil. Catheter is introduced through the jugular vein using a 8F introducer. Connection cables will be tunnelled to the base of the neck. At this area the cables are externalized. The goat will wear a jacket to prevent any damage to the recording electrodes.

Relevante literatuur

[1] Wieneke H, Konorza T, Erbel R, Kisker E. Leadless pacing of the heart using induction technology: a feasibility study. Pacing Clin Electrophysiol. 2009; 32(2):177-83

[2] Lee KL, Tse H, Echt DS, Lau C. Temporary leadless pacing in heart failure patients with ultrasound-mediated stimulation energy and effects on the acoustic window. Heart Rhythm 2009;6:742–748.

[3] Arnsbo P, Moller M. Updated appraisal of pacing lead performance from the Danish Pacemaker Register: The reliability of bipolar pacing leads has improved. Pacing Clin Electrophysiol 2000; 23:1401-1406.

[4] Smit J, Korup E, Schønheyder HC. Infections associated with permanent pacemaker and implanted cardioverter-defibrillator devices. A 10-year regional study in Denmark. Scand J Infect Dis. 2010 Sep;42(9):658-64.

[5] Sweeney MO, Prinzen FW. A New Paradigm for Physiologic Ventricular Pacing. J Am Coll Cardiol 2006; 47:282– 8.

[6] Biffi M, Boriani G: Phrenic stimulation management in CRT patients: are we there yet? Curr Opin Cardiol 2011; 26:12-16.

[7] Van Deursen C, Van Geldorp I, Rademakers, L.M. Van Hunnik A, Kuiper M, Klersy C, Auricchio A, Prinzen FW. Left ventricular endocardial pacing improves resynchronization therapy in canine LBBB hearts. Circulation: Arrhythmias and Electrophysiology; 2009: 2:580-587

University Maastricht

Faculty of Health, Medicine
and Life Sciences

Dierexperimenten Commissie

DEC

Aan:

, voorzitter
p/a Secretariaat DEC-UM
Postbus 616
NL-6200 MD Maastricht
Telefoon: 043

Uw referentie:

Onze referentie :

Maastricht, 31-08-2011

Geachte Onderzoeker,

Uw projectaanvraag: "*Leadless cardiac pacing using magnetic induction technology*", is op de DEC vergadering van 26 augustus 2011 besproken.

De DEC heeft een aantal vragen en opmerkingen:

- De DEC wenst een betere onderbouwing van de alternatieven bij punt 3.
- Bij punt 10a vraagt de DEC zich af wat bedoeld wordt met het vraagteken bij de "Induction anesthesia".

Gelieve eventuele vragen te beantwoorden in **een brief en indien noodzakelijk** Uw project **aan te passen en duidelijk de aanpassingen grijs te markeren.**

Uw project staat bij de DEC geregistreerd onder nummer 2011-113, gelieve dit nummer in verdere correspondentie te vermelden.

Hoogachtend,

Voorzitter DEC-UM

From:
Sent: woensdag 31 augustus 2011 12:11
To:
Subject: Re: Project 2011-113-w
Attachments: DEC2011-113revision.docx

Beste

Zie hier de gecorrigeerde versie van DEC 2011-113.
De beide suggesties zijn opgevolgd. Punt 3 is meer uitgebreid en de typefout van het vraagteken bij 11 is verwijderd.
Ik hoop dat de herziene versie niet hoeft te wachten voor goedkeuring tot de volgende vergadering, maar dat voorzitter en secretaris dit voor hun rekening kunnen nemen.
Omdat we druk met de planning bezig zijn, kun je me laten weten op dit laatste ook zo is?
Met vriendelijke groet

ogy

P.O. Box 616
6200 MD Maastricht
The Netherlands
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From: " ( )" <
Date: Wed, 31 Aug 2011 11:04:11 +0200
To: F >
Subject: Project 2011-113-w

Geachte onderzoeker,

Uw projectaanvraag is in de DEC-UM vergadering van 26 augustus 2011 besproken.

De uitslag treft u aan in bijgaand attachment.

Voortaan zult u uit efficiency overweging geen schriftelijke bevestiging meer ontvangen per post wanneer het een wijzigingsbrief betreft.

De DEC verzoekt U in een brief de vragen van de DEC te beantwoorden en de wijzigingen in het protocol duidelijk grijs te markeren, zodat het bij het kopiëren ook zichtbaar is.

Met vriendelijke groet namens DEC-UM:

Ambtelijk Secretaris Dierexperimentencommissie

Postbus 616 3, 6200 MD Maastricht
T 043
E-mail:

Werktijden: Ma-Di-Wo-Do: van 08.00 uur tot 16.00 uur

Maastricht University

Faculty of Health, Medicine and Life Sciences

Aan:

Ons kenmerk	*Doorkiesnummer*	*Maastricht*
	043-	05-09-2011

Project: *Leadless cardiac pacing using magnetic induction technology.*

Verantwoordelijk onderzoeker (VO):

Namens de Vergunninghouder van de DEC-UM, delen wij u mede dat voornoemd project aan de ethische toetsingscriteria voor proefdiergebruik voldoet.
De DEC maakt geen bezwaar tegen uitvoering van dit project zoals aangevraagd en geeft een positief advies.

Projectnummer:	2011-113
Diersoort:	geit
Aantal dieren:	20
Einddatum:	31-08-2015

Uw project staat bij de DEC en CPV geregistreerd onder bovenstaand nummer. Gelieve dieren, die voor dit project bestemd zijn, ook onder dit nummer aan te vragen.

Voorzitter DEC-UM

Vicevoorzitter DEC-UM

DEC-UM
Voorzitter DEC-UM

p/a secretariaat DEC-UM

Secretariaat DEC-UM
T (043)

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