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総合分担研究報告書

慢性心不全の予後を改善するための非侵襲で安全・安心な無痛性 ICD の実用化臨床試験
低侵襲電極植え込み技術の開発および電極の心機能へ与える影響の評価

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研究要旨：
高齢人口の増加にともない、循環器疾患が爆発的に増加（日本：3500 万人、世界：10 億人）するなかで、最終像である慢性心不全が激増している。しかしながら、慢性心不全の 5 年生存率は 50%に満たず、新たな治療法の開発は人類の急務である。近年、植込型除細動装置（ICD）治療による慢性心不全の予後改善が報告され、機器治療に対する期待が高まっている。このような背景のなかで、我々は厚生科研（H15-19）の支援を受け、従前の ICD の限界を克服すべく、極めて高度な付加機能（①迷走神経刺激＝細動なし、②即時診断＝意識消失なし、③超低電力除細動＝苦痛なし、④遠隔モニタ＝状態不明なし）を有した次世代 ICD の開発を行ってきた。本研究はこの成果を基盤に、従前の ICD 機能を遙かに凌駕する安全安心な無痛性 ICD（超 ICD）を完成し、実用化に向けた臨床試験を行うことを目的とする。
本分担研究は、現在開発中の超低電力除細動のための低侵襲な電極植え込み技術の開発および電極の心機能へ与える影響を評価することを目的とする。

A. 研究目的

循環器疾患が爆発的に増加（日本：3500 万人、世界：10 億人）するなかで、最終像である慢性心不全も激増している。患者数は欧米では 1150 万人を数え、毎年 55 万人が死亡している。わが国でも患者数は 100 万人を超える。医学の進歩により心不全の生命予後は改善してきたが、現在でも５年生存率は 50%に満たず、新たな治療法の開発は急務である。

一方、植え込み型デバイス（ICD）は低心機能患者の予後を改善する。しかしながら、従前の ICD は心室細動の抑制はできず、意識消失を防ぐこともできない。その上、大電力除細動を行うため、誤動作の際の著しい苦痛があり、患者の QOL は極端に悪い。申請者はこれまで厚生科研の支援を受け、従前の ICD の限界を克服する超 ICD の開発を行ってきた。本研究はその実用機を開発することを目的とする。

本研究では超低電力除細動のための電極が開発中されている。如何に除細動閾値が低い優れた電極でも、電極そのものが心機能に悪影響を与える可能性がある。さらに全身状態不良の患者に対し低侵襲な方法で安全かつ確実にその電極を装着できなければ治療法として確立しえない。本分担研究は低侵襲電極植え込み技術の開発と、電極の心機能へ与える影響を評価することを目的とする。

B. 研究方法

1. 低侵襲電極植え込み法の開発に関する研究①胸腔鏡下電極植え込み（平成 20～22 年度）：
成犬（体重 15kg）を用いた。仰臥位にて右胸部に 3 箇所の胸腔鏡用ポート（10mm）を挿入する。胸腔内での作業空間を確保するため、片肺換気や胸郭吊り上げなどの手法を試したが、最終的には内視鏡用送気装置により二酸化炭素をポートから胸腔内に送気し、術側の肺を軽度虚脱させることで両肺換気継続下での手術視野確保を完成させた。胸腔内のすべての操作は内視鏡操作（VISERA Pro システム、Olympus 社）で施行した。右胸腔内の心膜面脂肪をソノサージ（超音波メス）にて剥離したうえで、ポートから挿入した除細動電極を心膜に固定した。心膜への除細動電極の固定は 5-0 プロレンを用い、ノットプッシャーを用いて四ヶ所結紮することで可能であった。左胸部にも同様の操作を行って除細動電極を左側心膜に固定した。最後に電極リードを皮下を通して腹部に導いた。徐細動閾値を測定して閉創する。
②心嚢膜内直視下電極植え込み(平成 23～24 年度)：仰臥位にて心窩部を約５cm 正中切開

し剣状突起を切除した後に心嚢内へ到達する。心膜吊り上げは二箇所で 5-0 プロリンを用いて行う。電極挿入可能なレベルまで心膜を切開。電極を心嚢膜内に挿入し透視補助下に位置を決定し、5-0 プロリンにて電極を心膜へ固定する。電極の形状上、現時点では 2 箇所ないし 3 箇所の固定で充分と考えられる。心膜吊り上げを解除したのち徐細動閾値を測定。心膜を閉鎖し、閉創。電極のリード部分は前胸壁と心膜の癒着を可及的に予防するため、それぞれ左右胸腔を通し側胸部から胸腔外へ出したのちに皮下を通して心窩部皮下作成したポケットに格納する。麻酔から覚醒させ、以後は飼育室にて管理し、1 ヶ月毎に閾値の変化を測定した。

2. 電極植え込みの心機能に与える影響評価

256 スライスの MDCT、コンダクタンスカテーテルあるいは超音波クリスタルを用い、慢性期の電極の心機能に及ぼす影響を評価した。閾値の最終評価の後に、心臓を摘出し電極による左心室の拡張特性に及ぼす影響を圧容積関係で評価した。左室容積は心室内にバルーンを挿入し正確にコントロールした。

C. 研究結果

1. 低侵襲な電植え込み

①胸腔鏡下電極植え込み：鏡視下手術では送気装置を用いることで片肺換気とすることなく良好な視野を確保でき、左右心膜除細動電極を植え込むことが可能であった。心負荷、呼吸への影響も少なかった。しかしながら慢性犬においては、電極周囲の癒着と閾値の経時的上昇が問題となった。また手術操作に長時間を要する事も問題と考えられた。

②心嚢膜内直視下電極植え込み：透視を補助的に用いる事で小さな術創での電極留置が可能であった。また、直視下に電極の挿入・固定が行えるため胸腔鏡下の手術に比べ手術操作が容易で手術時間も著明に短縮した。術中の心負荷、呼吸への影響は少なかった。慢性犬においては癒着による閾値の経時的上昇が問題となった。

2. 心機能に与える効果

電極の植え込みは慢性期の収縮特性を変化させなかった。同様に、電極の植え込み部位を適切に選ぶことで、電極は拡張機能に有意な影響を与えないことが明らかになった。

D. 考察

1. 低侵襲な電極植え込み

犬は胸腔の左右径が小さく内視鏡の視界が不良であり、内視鏡操作が困難である。ヒトにおいても、末期慢性心不全では著明な心拡大を呈するため、やはり胸腔内の作業空間が十分にとれないことが予想される。そのため本研究では肺圧排デバイスを併用した胸壁吊り上げ法や、内視鏡用送気装置により二酸化炭素を送気して肺を虚脱させる方法などを用い内視鏡下に電極の植え込みを行ってきた。しかしながら手術操作が煩雑でかつ手術時間が長くなる傾向にあり、慢性実験では心膜面の剥離操作により癒着や結合組織の増成が生じ、これによってもたらされる閾値上昇が問題となった。

そこで、平成 23 年度より心窩部小切開による心嚢内直視下での電極植え込みを考案した。可視範囲が狭く電極の位置を俯瞰的に見る事が出来ないが、透視装置を併用する事で正確な電極留置が可能である事が確認できた。また電極の形状を工夫する事で、可視範囲の 2 箇所固定でも電極ずれを回避できる事が確認された。

心窩部小切開から心嚢内に到達する手法は心タンポナーデ解除術や小児の心筋電極植え込み術等で実際に臨床でも行われており、本実験においても有効かつ安全に施行し得た。この方法は内視鏡手術と比較してより低侵襲で安全な植込みが実現できると考えられた。

2. 心機能に与える効果

左心室の圧容積関係という、最も信頼性の高い評価法を用いた。その結果、除細動電極の植え込みでは、慢性期においても収縮機能も拡張機能も有意な変化が起きないことが示された。このことは心不全を対象とした除細動装置において、心機能を悪化させることなく電極が植え込めることを意味しており、臨床的な価値は極めて大きい。

E. 結論

今回、超低電力除細動電極を低侵襲で植え込むための慢性動物実験を行った。犬を使用することの解剖学的なデメリットはあるものの技術的には十分可能である。電極による心機能への影響は有意ではない。閾値上昇の原因となる癒着に関しても手術手技の工夫で最小限に抑える事が可能であると考えられる。

F. 健康危険情報

なし

G.研究発表

G-1.論文

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29. 砂川賢二：循環制御メカニズム研究の進歩。第 29 回日本循環制御医学会総会（平成 20 年 5 月 10 日、横浜）

30. 伊藤浩司、廣岡良隆、砂川賢二：食塩負荷で生じる圧負荷モデルでの左心機能低下に脳内 ENaC を介した脳脊髄液内 Na 濃度上昇によって生じる交感神経活性化が関与する。第 29 回日本循環制御医学会総会（平成 20 年 5 月 10 日、横浜）

31. 砂川賢二：変貌する 21 世紀の医学：バイオニック医学による循環制御。第 31 回日本生体医工学会中国四国支部大会（平成 20 年 10 月 18 日、岡山）

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G-3.新聞報道

掲載紙:西日本新聞
掲載年月日:2008年12月17日
タイトル:「先端的医療早期実現へ九大など開発特区に」

掲載紙:読売新聞
掲載年月日:2008年12月17日
タイトル:「九州大学医学部先端医療開発特区に採択」

掲載紙:科学新聞
掲載年月日:2008年11月28日
タイトル:「先端医療開発特区の課題決定」

掲載紙:西日本新聞
掲載年月日:2008年11月19日
タイトル:「短信　初のスーパー特区に24件」

掲載紙:日本経済新聞
掲載年月日:2008年11月18日
タイトル:「先端医療技術実用化促す」

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掲載年月日:2010年4月20日
タイトル:「次世代ICD共同開発」

H.知的所有権の取得状況

1. 砂川賢二:Cardiovascular disease therapy device（米国）2009 年 3 月 19 日、61/161456
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総合分担研究報告書

慢性心不全の予後を改善するための非侵襲で安全・安心な無痛性 ICD の実用化臨床試験 デバイスサイクルの計画と調整 臨床試験の実行に関する研究

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研究要旨：ICD は植込み型医療機器であり且つ生命に直接関わるため GHTF class IV device としてどの国においても機器の中では最も厳しい薬事規制を受けている。

国内初の ICD 開発を円滑に進めるため、医療機器全般でも承認が米国より遅れている本邦の現状を打開するため、欧米における規制制度との比較、デバイスラグの原因調査、短いライフサイクルに対応しようとする医療機器規制変化に合わせた臨床開発法について調査した。

臨床試験データの蓄積がある欧米では比較的小さな試験でも科学的比較が可能である。十分なサイズの治験が困難な医療機器を含めて市販前評価を促進する種々の改革が本邦においてもされつつあるが十分とは言いがたい。一方で安全性・有効性の担保を市販後レジストリーで行うことが非常に有効である事が事例から示された。

ICD のような高リスク医療機器の臨床開発は治験だけに頼るのではなく、市販前、市販後にわたって質の高い臨床試験データをバランスよく収集・利用できる方法を規制当局と協力しながら今後も工夫し、本邦における医療機器開発を促進して行くことが肝要である。

A.研究目的

ICD は植込み型医療機器であり且つ生命に直接関わるため GHTF class IV device としてどの国においても機器の中では最も厳しい薬事規制を受けている。臨床開発法に関しては近年 CRT 機能の付加以外に大きな変化はなかったため以前の試験成績に立脚した開発が欧米では行われており、大規模試験などは殆ど行われていない。

国内初の ICD 開発を円滑に進めるため、医療機器全般で十分なサイズの治験が困難で、承認が米国より遅れている本邦の現状を打開するため、欧米における規制制度との比較、デバイスラグの原因調査、短いライフサイクルに対応しようとする医療機器規制変化に合わせた臨床開発法について調査した。

B.研究方法

B-1. ICD の薬事規制に関する欧米との比較

ICD および高リスク医療機器の規制文書、ガイダンスなどの整備状況を欧米と比較した。

B-2. 本邦で医療機器開発が遅れる原因、その対策の調査

デバイスラグの原因とその対策の調査、本邦における医療機器臨床開発の促進法について調査、考案した。

C.研究結果

C-1. ICD の薬事規制に関する欧米との比較

・ガイダンスドキュメントについて

本邦では開発されたことがない ICD の開発ガイダンスは存在しない。「植込み型心臓ペースメーカ等承認基準の制定について」(平成 19 年 3 月 2 日、薬食発第 0302004 号、厚生労働省医薬食品局長通知)が最も近い文書である。

米国においては CDRH, FDA より”Functional Indications for Implantable Cardioverter Defibrillators”というガイダンス案が 2005 年に公布され device class として大まかに何を満たすべきであるかが記載されていたが 2011 年 4 月 27 日に案のまま取り下げられた。

欧州においては多数の国の規制を EC が制御しているなどの理由で一般に規制が緩やかである。EU から 90/385/EEC という Active implantable medical device に関する医療機器指令（通称 AIMDD）が公布されており、implantable cardiac pacemakers, implantable defibrillators, leads, electrodes, adaptors for the above などをカバーしている。規格については British Standard Institution から EN45502 などの文書が出ており事実上の標準となっている。

・米国 PMA, sPMA, 510(k)の運用について
米国での class III (GHTF III-IV に相当)機器は原則として PMA（市販前承認申請）が必要とされ、臨床試験が必須となるが、複数の別経路も存在する。US GAO（政府監査院）がこの点を不適切として FDA に改善を求めている。2011 年に第三者委員会は８つの具体的な改善点を提言し、市販後調査、登録による安全対策などを中心とした抜本的な改革、class III については 510(k)で認証されないよう求めている。

C-2. 本邦で医療機器開発が遅れる原因、その対策の調査

・ デバイスラグについて

アメリカ商工会議所日本支部（ACCJ）による「2008 年デバイスラグ調査」に詳述されているように、その原因は多岐にわたる。同報告書には産側から官側への要望が多数提言されているが、以下の項目については既に対応がなされている。

- 製品の安全性や有効性に影響しない一変を不要とする
- 米国のモジュラー制度に類似したシステムを導入
- 新規と後発の審査を分離する。3 トラック制導入
- 民間からの積極的な採用も含め審査員を大幅に増員

2008 年発表の PMDA「第２期中期計画に向けた論点について」に記載された「デバイス・ラグの実態（日米の比較）」（2003-2005 年度）では米国と比較し新医療機器申請前ラグが 12 ヶ月、申請後ラグが 7 ヶ月程度と合わせて総ラグが 19 ヶ月程度となっている。ACCJ 調査報告では 2006 年の PMDA 調査（上記中期計画報告での調査から米国対応製品のみを集計していると思われる）と比較されている。この 2 年間の間に審査が速くなり申請後ラグが減少したかわりに、申請前ラグが増大し、結果的に総ラグがほぼ同じになったように見える。種々の要因により申請後から申請前にラグがシフトしたのみであると分析している。

厚労省はデバイスラグ解消の一助として 2006 年に「医療ニーズの高い医療機器の早期導入に関する検討会」を設定し、選定された海外既承認医療機器の国内早期承認を後押ししてきた。リスクの高い治療機器、植込み型 class IV の要望が多く、選定された大部分を占めている。このようなハイリスク機器は国内開発が困難であることを意味している。

・GCP 省令・運用通知の見直し

オーバークオリティと批判の多かった本邦における GCP 運用（J-GCP と呼ばれる）が H24 年 12 月に見直され、手続きが一部簡素化された。

・先進医療制度

H24 年 7 月に厚労省医政局長、保険局長、医薬食品局長連名の通知（薬食発 0731 第 2 号など）として先進医療の枠組みが改められた。医薬食品局長が通知発出をしていることにより先進医療の成績をもって薬事承認の１方法と成り得る可能性が示された。

・拠点整備（橋渡し研究拠点、臨床研究中核病院）

H19 年から文科省橋渡し研究支援プログラム、H24 年から厚労省臨床研究中核病院整備事業により選定された大学などの研究機関においてシーズから臨床研究、治験に至るまで自ら実施できる基盤が整備されつつある。これら国際基準の質の高い臨床試験（ICH-GCP 試験）を行い得る機関に限って、その試験成績を薬事承認に使えるようにする方向で検討されている。

・市販後レジストリーによる安全性・有効性の担保

植込み型補助人工心臓 VAS については心移植の停滞、実質的に使用可能なものが国循型の体外式のみであったことから、非常に要望が強く、「医療ニーズの高い医療機器等の早期導入に関する検討会」においても早期導入が推奨された。その結果として DuraHeart、EvaHeart は少数例の試験成績で H22 年 12 月に承認された。

このような少数での市販前評価を補足する手段としてこの２機器については下記の用な承認条件がつけられた。

「再審査期間においては関連学会と連携の上、継続治験後の症例も含む全例を対象に使用成績調査を行うとともに植込まれた患者の長期予後を観察しその解析結果を報告する事」

PMDA 安全第一部 調査分析課が関連学会・研究会（7 団体）、業界団体、関連企業の関係者と共同で、全国の植込み実施施設の参加による多施設共同研究としてレジストリー「日本における補助人工心臓に関連した市販後のデータ収集（J-MACS : Japanese registry