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EDITORIAL

ARE NEW BOTTLES FIT FOR OLD WINES?

<http://www.lebanesemedicaljournal.org/articles/67-1/editorial1.pdf>

The Lebanese Medical Journal (LMJ) has a new editorial board. Some members are from the old guard while others are new. The newly assigned team has a hard task of continuing the outstanding job done by its predecessor and fulfilling the vision drawn years ago of making this journal the hub for scientific publications in the region. The Lebanese Medical Journal (since 1948 as *la Revue Médicale Libanaise*) is more than 70 years old. That makes it an old journal indexed in PubMed and Medline since 1951. It is practically one of the rare journals in the Middle East with such a history.

The Lebanese Medical Journal benefited throughout the years of Lebanon's prosperity in the sixties and the beginning of the seventies when our country was the Middle East Switzerland of the East in many domains, especially in medicine and culture. The number of papers published in LMJ journal increased and peaked in 1974 up to 93. It was the highest rate of publication ever recorded in LMJ. While looking at PubMed for the themes of papers published in LMJ at that time, I was pleasantly surprised that critical articles and outstanding authors were included in the "1974 class". One of the authors was Harold Nixon, who was one of the most innovative pediatric surgeons [1]. His main contributions were in anorectal diseases in children, especially Hirschsprung's disease; he published in particular two papers in 1974 on "the present status of Hirschsprung's disease" and "anorectal anomalies." LMJ included not only case reports but many interesting series and original articles, at a time when publishing was not a trend [2,3].

The civil war that ravaged Lebanon between 1975 and 1990, killed not only innocents but also culture and science. Thirty-one papers were published in 1975, none between 1976 and 1979, interrupted by a honeymoon of 22 papers in 1980 to go back to none between 1981 and 1985. Between 1986 and 1991 thirty-two papers were discontinuously published, i.e. roughly six papers per year.

The pace of publication was no more interrupted afterwards and that, thanks to the endeavor and significant efforts of the successive editorial boards that worked "pro bono publico," giving their time and expertise to provide visibility to the LMJ.

LMJ website was created on March 1, 2007, and a direct web submission was meant to be effective. This procedure is going to be reactivated to facilitate the process.

This year, the first issue is a special one on cardiology edited by a colleague from the American University of Beirut, Marwan Refaat, and drafted jointly by many authorities in rhythmology. By the end of this issue, a guideline for practice is published on *Brucella*, by international authorities in this field. In every issue, whenever applicable, we will try to include guidelines and recommendations in each specialty backed by authorities and scientific societies.

The new editorial board is committed to reduce the delay of answering to 5-6 weeks and to publish within the same calendar year papers accepted before July or maximum the following year within the first two issues.

My gratitude goes to Michèle Valligny and Elie Ammar, the production backbone of the journal for years. I sincerely appreciate their effort and their commitment towards the LMJ always done at a very minimal cost with maximal results.

Bottom line: our journal is still alive and doing well.

We are trying to look to the future and to be ambitious. We hope to focus on building a brand-new journal with international exposure and higher visibility. This will require a lot of effort from the whole medical community to fulfill our goal.

Like a vintage, LMJ is a heritage that the whole Lebanese medical community entrusted us. We must thrive on finding a new bottle likely to withstand the test of time and eventually change it, when needed, to preserve the old wine.

David ATALLAH, MD, MSc*
Editor in chief

-
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- * Department of Obstetrics and Gynecology, Hôtel-Dieu de France University Hospital, Saint-Joseph University, Beirut, Lebanon.

GUEST EDITORIAL

A SPECIAL ISSUE ON CARDIAC ARRHYTHMIAS

<http://www.lebanesemedicaljournal.org/articles/67-1/editorial2.pdf>

The 2017 European Heart Rhythm Association (EHRA) White Book was published with cardiac implantable electronic device (CIED) and interventional electrophysiology data on European Society of Cardiology (ESC) member countries [1].

Lebanon, an ESC member country, did not have data [1]. Hence, there was an unmet need to have CIED and interventional electrophysiology data from Lebanon. The last data reported from Lebanon were from 2010 and 2013 [2,3]. This issue will address this gap and include data on CIED and cardiac ablation from Lebanon as well as epidemiology from atrial fibrillation enrolled in a single center registry.

This issue includes original manuscripts with collaboration with the University of Pittsburgh Medical Center (Pittsburgh, Pennsylvania - USA) as well as the University of California San Francisco Medical Center (San Francisco, California - USA). It also includes a review on the association of diabetes, atrial fibrillation and ventricular arrhythmias.

Marwan M. REFAAT, MD*

Guest editor

1. Raatikainen MJP, Arnar DO, Merkely B, Nielsen JC, Hindricks G, Heidbuchel H, Camm J. A decade of information on the use of cardiac implantable electronic devices and interventional electrophysiological procedures in the European Society of Cardiology Countries: 2017 Report from the European Heart Rhythm Association. *Europace* 2017 Aug 1; 19 (Suppl 2): ii1-ii90.
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- * American University of Beirut Faculty of Medicine and Medical Center (AUBMC). Associate Professor of Medicine. Director, Cardiovascular Fellowship Program. Department of Internal Medicine, Cardiology Division/Cardiac Electrophysiology Section, Department of Biochemistry and Molecular Genetics.
e-mail: mr48@aub.edu.lb OR marwanrefaat@alumni.harvard.edu

CARDIAC ARRHYTHMIAS

CARDIAC IMPLANTABLE ELECTRONIC DEVICES IN LEBANON

<http://www.lebanesemedicaljournal.org/articles/67-1/original1.pdf>

Marwan M. REFAAT^{1*}, Mohammad SABRA¹, Assaad ABDEL AHAD², Malek KHATIB³, Mario NJEIM⁴
Maurice KHOURY¹, Charles JAZRA⁵, Johny ABOUD²

Refaat MM, Sabra M, Abdel Ahad A, Khatib M, Njeim M, Khoury M, Jazra C, Abboud J. Cardiac implantable electronic devices in Lebanon. *J Med Liban* 2019; 67 (1): 4-7.

Refaat MM, Sabra M, Abdel Ahad A, Khatib M, Njeim M, Khoury M, Jazra C, Abboud J. Dispositifs électroniques à implantation cardiaque au Liban. *J Med Liban* 2019; 67 (1): 4-7.

ABSTRACT • Objectives: The 2017 European Heart Rhythm Association (EHRA) White Book was published with cardiac implantable electronic device (CIED) data on European Society of Cardiology (ESC) member countries. Three countries (Lebanon, Libya and Syria) of the 56 ESC member countries did not have data. Hence, there was an unmet need to have CIED data estimate in Lebanon. **Methods:** Data from companies providing CIEDs in Lebanon was collected to have trends on CIED implants in Lebanon from the beginning of 2013 till the end of 2017. **Results:** In 2017, the total number of CIED implants was 1656: 983 (59.4%) were pacemakers and 673 (40.6%) were ICDs. Most CIED implants are dual chamber pacemakers. There has been a rise in the implantation of ICDs in Lebanon from 2013 till 2017. For instance, in 2013 the prevalence of CRT-D, dual chamber ICD, and single chamber ICD were 214, 64, and 268. In 2017, the prevalence of the different types of ICD became 243, 75, and 355. **Conclusion:** CIED implants have increased over the last several years in Lebanon in parallel with the number of cardiac electrophysiologists. It is important to have a national registry of CIED implants in Lebanon which will require financial support for its maintenance.

Keywords: pacemakers; implantable cardioverter defibrillators; ICDs; cardiac implantable electronic devices; CIEDs

RÉSUMÉ • Objectifs: Le livre blanc 2017 de l'European Heart Rhythm Association (EHRA) a été publié avec les données des dispositifs électroniques à implantation cardiaque (CIED) dans les pays membres de l'ESC (Société européenne de cardiologie). Trois pays (Liban, Libye, Syrie) parmi les 56 pays membres de l'ESC n'avaient pas de données. Il était donc nécessaire de disposer d'une estimation du nombre de CIED au Liban. **Méthodes:** Les données des entreprises fournissant des CIEDs au Liban ont été collectées pour dégager les tendances des CIEDs au Liban du début de 2013 à fin 2017. **Résultats:** En 2017, le nombre total d'implants CIED était de 1656: 983 (59,4%) étaient des stimulateurs cardiaques et 673 (40,6%) des défibrillateurs. La plupart des CIEDs sont des stimulateurs cardiaques à double chambre. Il y a eu une augmentation du nombre de défibrillateurs automatiques implantables (DAI) au Liban de 2013 à 2017. Par exemple, en 2013, la prévalence du DAI à triple chambre, DAI à double chambre, DAI à chambre unique était 214, 64 et 268. En 2017, la prévalence des différents types de DAI est devenue 243, 75, et 355. **Conclusion:** Les implants CIED ont augmenté au cours des dernières années au Liban et connu une croissance parallèlement au nombre de rythmologues. Il est important de disposer d'un registre national d'implants CIED au Liban, ce qui nécessitera un soutien financier pour son entretien.

Mots-clés: stimulateurs cardiaques; défibrillateurs automatiques implantables; ICDs; dispositifs électroniques à implantation cardiaque; CIEDs

INTRODUCTION

Sudden cardiac death (SCD) is a rising and a major public health concern in developed and developing countries. In the US, SCD claims around 450,000 victims annually [1]. Many studies have established the efficacy and importance of implantable cardioverter defibrillator (ICD) therapy in the prevention and reduction of mortal-

ity from SCD [2-4]. However, despite the established guidelines about the ICD in SCD, the implantation rates vary between countries.

Lebanon is considered part of the European Society of Cardiology (ESC) as a non-European ESC country and has been involved in the statistics released by the society concerning ICD prevalence, implantation rate, and indications. According to the statistics released by the ESC on 2013, Lebanon has 73 implantations of ICD per million inhabitants which is below the median (82) and the mean (100) compared to other European countries [5]. Lebanon falls in the lower half of the ESC countries regarding the incidence of ICD implantations per year. There are several explanations of the discrepancies in ICD implantation rates between countries. One could be that countries implanting more ICDs per year have higher replacement rates in the subsequent years.

¹Department of Internal Medicine, Division of Cardiology, American University of Beirut Medical Center, Beirut, Lebanon.

²Electrophysiology Unit, St George Hospital University Medical Center, Beirut, Lebanon.

³Division of Cardiology/Electrophysiology, Military Hospital, Beirut, Lebanon.

⁴Division of Cardiology/Electrophysiology, Hôtel-Dieu de France/ Université Saint-Joseph, Beirut, Lebanon.

⁵Division of Cardiology/Electrophysiology, Hôpital Saint-Joseph des Sœurs de la Croix, Dora, Lebanon.

*Corresponding author: *Marwan M. Refaat, MD.*

e-mail: mr48@aub.edu.lb / marwanrefaat@alumni.harvard.edu

Another explanation could be that countries with highest ICD implantation rates are those with a healthcare system favorable of SCD prevention.

There is an absence of an official registry regarding cardiac implantable electronic devices (CIEDs) [Pacemakers and implantable cardioverter defibrillators] in Lebanon. It was estimated that around 900 CIED implantations are performed yearly in Lebanon. Among the 900 yearly implanted devices, around 300 are ICD and/or CRT-D (cardiac resynchronization therapy with defibrillator). In addition, device implantations including ICD are done mainly by cardiologists and around one third are performed by surgeons.

Device follow-ups are performed by electrophysiologists in around 60% of the cases, while the remaining are performed by industry technicians and non-electrophysiologist physicians [6].

The 2017 European Heart Rhythm Association (EHRA) White Book was published with CIED data on ESC member countries [7]. Three countries (Lebanon, Libya and Syria) of the 56 ESC member countries did not have data. Hence, there was an unmet need to have CIED data estimate in Lebanon

METHODS

Data from companies providing CIEDs in Lebanon was collected to have trends on CIED implants in Lebanon from the beginning of 2013 till the end of 2017.

RESULTS

In 2017, the total number of CIED implants was 1656: 983 (59.4%) were pacemakers and 673 (40.6%) were ICDs. Most CIED implants are dual chamber pacemakers (Figures 1 and 2).

There has been a rise in the implantation of ICD in Lebanon from 2013 till 2017 (Figure 3). For instance, in 2013 the prevalence of CRT-D, dual chamber ICD, and single chamber ICD were 214, 64, and 268. In 2017, the prevalence of the different types of ICD became 243, 75, and 355 (Figure 3).

DISCUSSION

This study fills an unmet need and fills the gap of providing recent data on CIED implants in Lebanon. The 2017 EHRA White Book was published with CIED data on ESC member countries with no data on Lebanon. Three countries (Lebanon, Libya and Syria) of the 56 ESC member countries did not have data in the 2017 EHRA White Book [7]. Hence, there was an unmet need to have CIED data estimate in Lebanon.

Our study shows a rise in CIED implants in Lebanon over the last few years with most CIED implants being dual chamber pacemakers. None of the implanted pacemakers in 2017 and in prior years was leadless. In August 2018, the first leadless pacemaker (Micra) in Lebanon was implanted at the American University of Beirut Medical

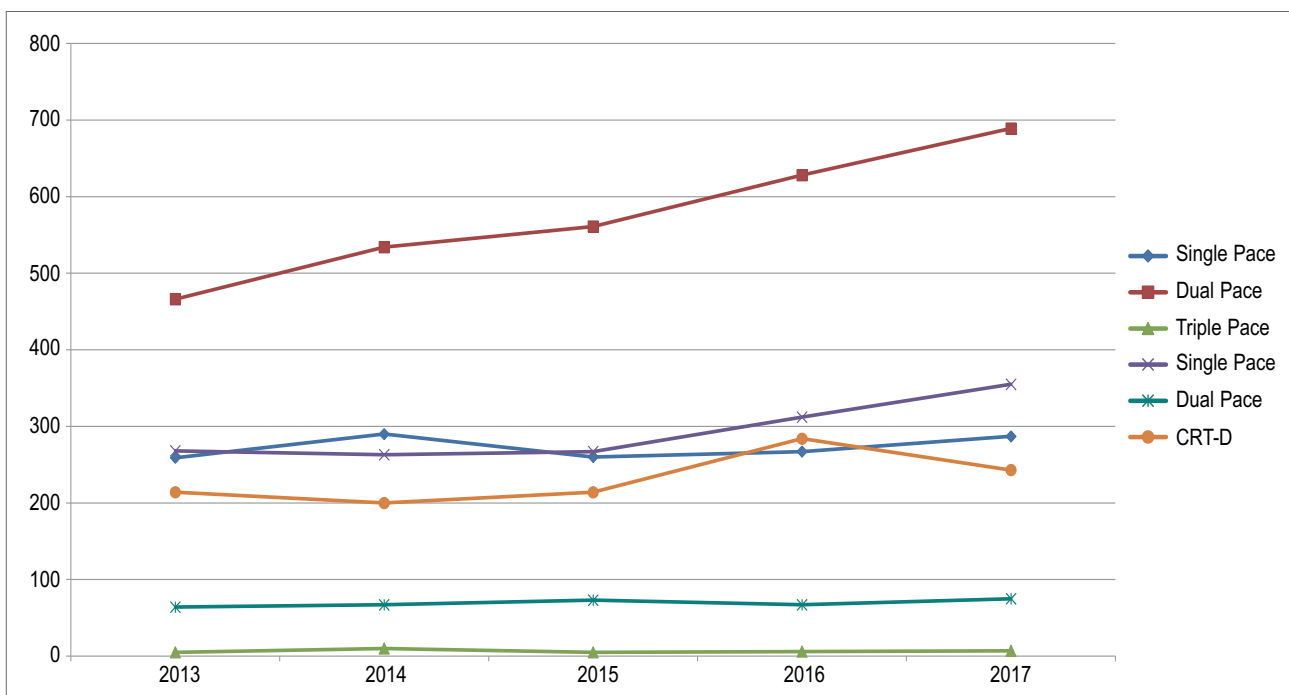


Figure 1. CIED implantation in Lebanon (2013-2017)

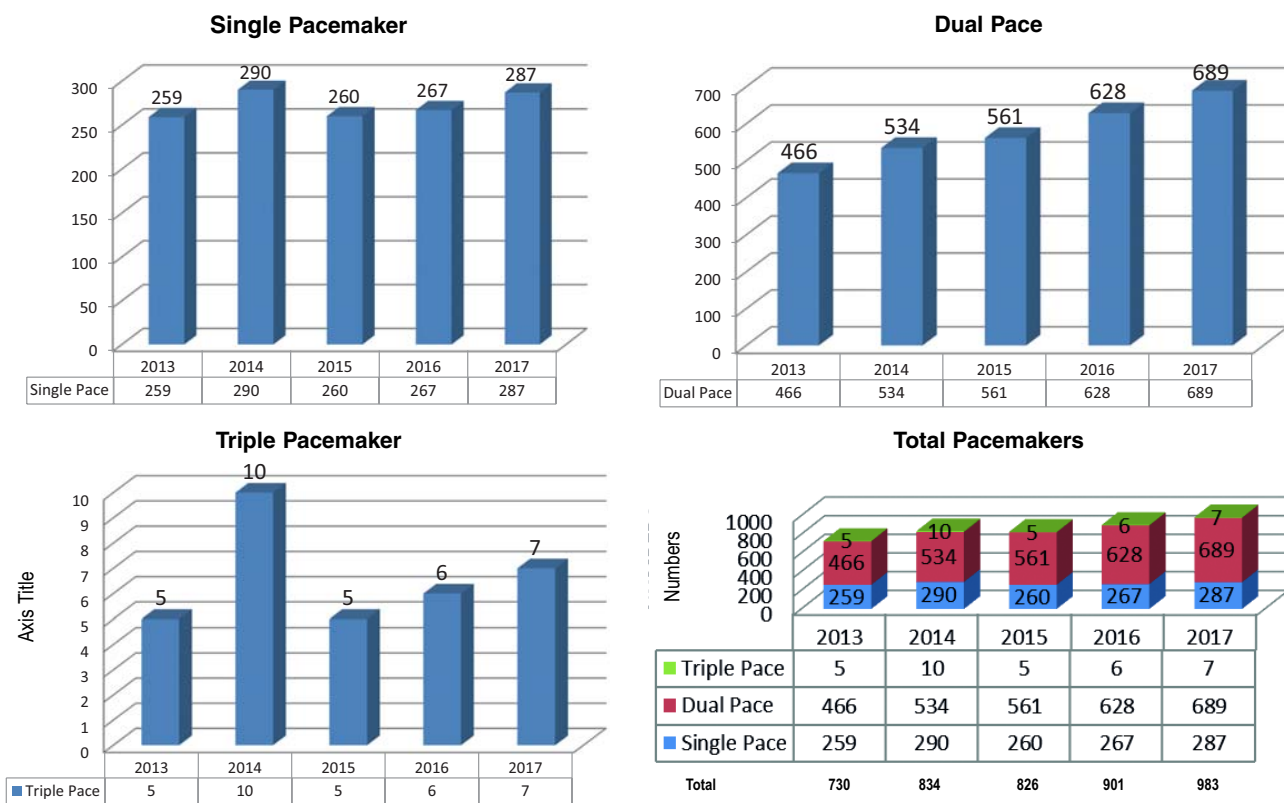


Figure 2. Pacemaker implantation in Lebanon (2013-2017)

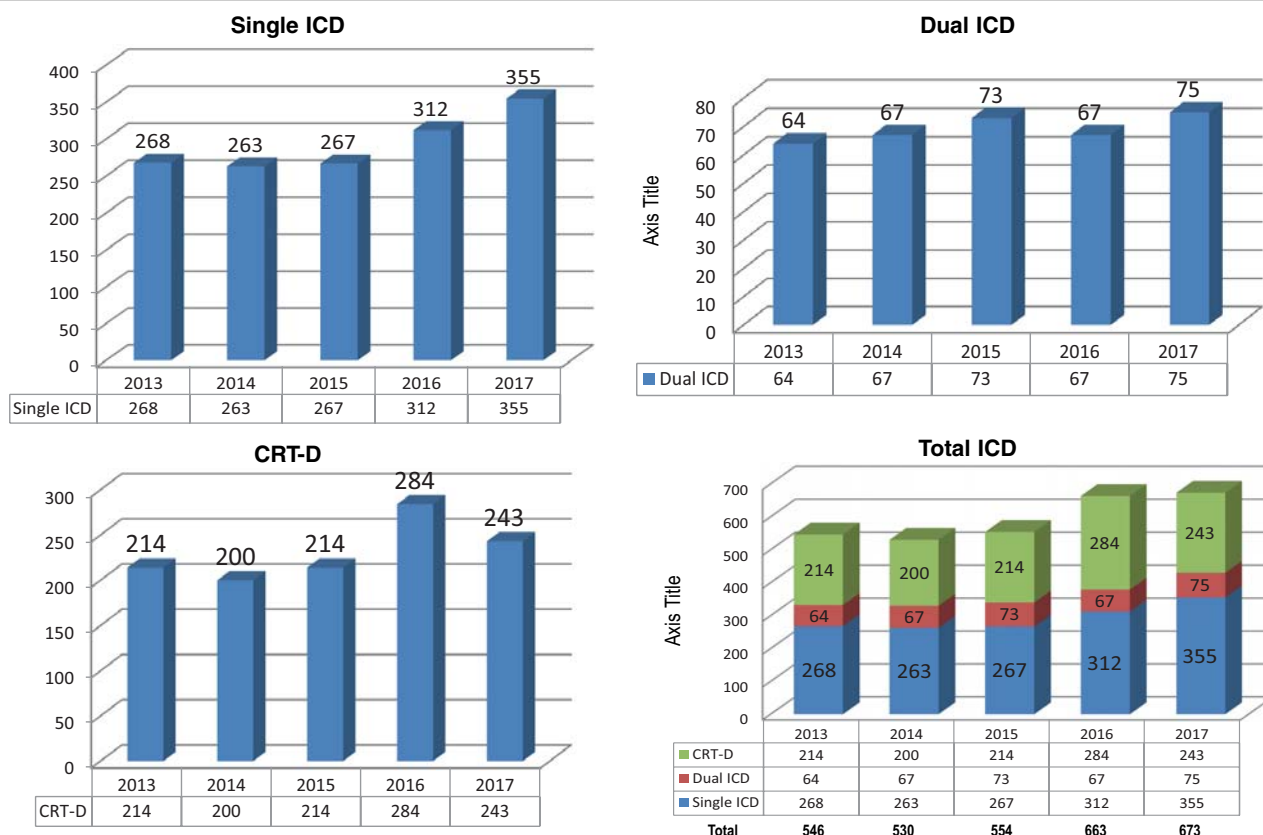


Figure 3. Implantable cardioverter defibrillator implantation in Lebanon (2013-2017)

Center (AUBMC). In April 2019, the first permanent HIS bundle pacemaker in Lebanon was successfully implanted at AUBMC.

This study shows an increase in the utilization of ICD in the Lebanese population which can be due to several reasons which include: population on the rise, increase in the lifespan of the population, better healthcare, improved diagnostic and procedural skills. A significant number of CIEDs in Lebanon are not supervised afterwards by a cardiac electrophysiologist [8].

There is a need of post implant device interrogation and programming to be always supervised by of a cardiac electrophysiologist to prevent complications [9].

There is sufficient evidence in the literature about the importance of ICD implantation in primary and secondary prevention of SCD. ICD implantation was shown to improve survival in patients with life-threatening ventricular arrhythmia. Several trials have investigated the role of ICD in secondary prevention of SCD, most notably were the Antiarrhythmics vs. Implantable Defibrillators (AVID) trial, the Cardiac Arrest Study Hamburg (CASH), and the Canadian Implantable Defibrillator Study (CIDS) [10-12]. Furthermore, the role of ICD implantation in primary prevention has been investigated and proven. Recent evidence suggests that ICD implantation improves survival in patients with left ventricular ejection fraction (LVEF) of 35% or less and New York Heart Association class II or III heart failure and those with a history of myocardial infarction and LVEF of 30% or less [4,13-14].

An ESC analysis has shown a significant correlation between the incidence of ICD implantation per million and the GDP ($r = 0.68, p < 0.0001$), the GDP per capita ($r = 0.79, p < 0.0001$), and the expenditure on health ($r = 0.69, p < 0.0001$). The type of the implanted ICD (single or dual chamber) was not significantly correlated to the GDP and expenditure on health. In addition, a weak correlation was found between ICD implant rates and the density of physicians. There was also a correlation between life expectancy rates and ICD implantation rates.

There was no association between healthcare indices like number of hospital beds and ICD implantation rates. Also, there was a significant influence of the presence of cardiac electrophysiology specialty on the ICD implantation rates [15]. CIED implants have increased over the last several years in Lebanon along with the number of cardiac electrophysiologists which reached around 20 [16].

CONCLUSIONS

CIED implants have increased over the last several years in Lebanon along with the number of cardiac electrophysiologists. It is important to have a national registry of CIED implants in Lebanon which will require financial support.

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CARDIAC ARRHYTHMIAS

STATUS OF ABLATION OF CARDIAC ARRHYTHMIAS IN LEBANON

<http://www.lebanesemedicaljournal.org/articles/67-1/original2.pdf>

Mohammad SABRA¹, Mario NJEIM², Malek KHATIB³, Marwan M. REFAAT^{1*}

Sabra M, Njeim M, Khatib M, Refaat MM. Status of ablation of cardiac arrhythmias in Lebanon. J Med Liban 2019; 67 (1): 8-9.

ABSTRACT • Objectives: The 2017 European Heart Rhythm Association (EHRA) White Book was published with interventional electrophysiology data on ESC member countries. Lebanon, an ESC member country, did not have data on cardiac ablation. Hence, there was an unmet need to have cardiac ablation estimate in Lebanon. **Methods:** Data from companies providing support for cardiac ablation in Lebanon was collected for the year 2017. **Results:** In 2017, the number of catheter ablations performed was close to 350. This is around 70 per million of Lebanese. There has been a significant increase, over 50%, in the 2010-2017 period: 50 to 60 ablation procedures were performed annually in 2010 (most of them for supraventricular tachycardias) and this increased to around 100 per year in 2013. **Conclusion:** Cardiac ablation procedures have increased over the last several years in Lebanon in parallel with the number of cardiac electrophysiologists. It is important to have a national registry of cardiac ablations in Lebanon which will require financial support for its maintenance.

Keywords : ablation; radiofrequency; cryoablation; cardiac arrhythmias

Sabra M, Njeim M, Khatib M, Refaat MM. Évaluation de l'ablation des arythmies cardiaques au Liban. J Med Liban 2019; 67 (1): 8-9.

RÉSUMÉ • Objectifs: Le livre blanc 2017 de l'European Rhythm Association (EHRA) a été publié avec des données d'électrophysiologie interventionnelle dans les pays membres de la Société européenne de cardiologie (SEC). Le Liban, pays membre de la SEC, ne disposait pas de données sur l'ablation cardiaque. Il y avait donc un besoin non satisfait d'avoir une estimation de l'ablation cardiaque au Liban. **Méthodes:** Les données des entreprises fournissant une assistance pour l'ablation cardiaque au Liban ont été collectées pour l'année 2017. **Résultats:** En 2017, le nombre d'ablations par cathéter réalisées était proche de 350. Cela représente environ 70 par million de Libanais. Il y a eu une augmentation significative de plus de 50% sur la période 2010-2017: 50 à 60 procédures d'ablation ont été effectuées chaque année en 2010 (la plupart pour des tachycardies supraventriculaires) et ont augmenté pour atteindre environ 100 par an en 2013. **Conclusion:** Les procédures d'ablation cardiaque ont augmenté au cours des dernières années au Liban, et connu une croissance liée au nombre de rythmologues. Il est important de disposer d'un registre national des ablations cardiaques au Liban, ce qui nécessitera un soutien financier pour son maintien.

Mots-clés : ablation; radiofréquence; cryoablation; arythmies cardiaques

INTRODUCTION

Ablation procedures of cardiac arrhythmias aim to eliminate the trigger or alter/eliminate the arrhythmogenic substrate in the atria or ventricles.

Data on cardiac ablation in Lebanon is lacking. The 2017 European Heart Rhythm Association (EHRA) White Book was published with interventional electrophysiology data on the European Society of Cardiology (ESC) member countries [1].

Lebanon, a non-European ESC member country, did not have data on cardiac ablation procedures [1]. Hence, there was an unmet need to have data estimate of cardiac ablation in Lebanon.

METHODS

Data from companies (Abbott and Biosense Webster) providing support for ablation procedures in Lebanon was collected for the year 2017.

RESULTS

In 2017, the number of catheter ablations performed was close to 350. This is around 70 per million of Lebanese. There has been a significant increase greater than 50% in the 2010-2017 period: 50 to 60 ablation procedures were performed annually in 2010 (the majority for supraventricular tachycardias) and this increased to around 100 per year in 2013 (Figure 1).

¹Department of Internal Medicine, Division of Cardiology, American University of Beirut Medical Center, Beirut, Lebanon.

²Division of Cardiology/Electrophysiology, Hôtel-Dieu de France Hospital, Université Saint-Joseph, Beirut, Lebanon.

³Division of Cardiology/Electrophysiology, Military Hospital, Beirut, Lebanon.

*Corresponding author: *Marwan M. Refaat, MD*

e-mail: mr48@aub.edu.lb OR

marwanrefaat@alumni.harvard.edu

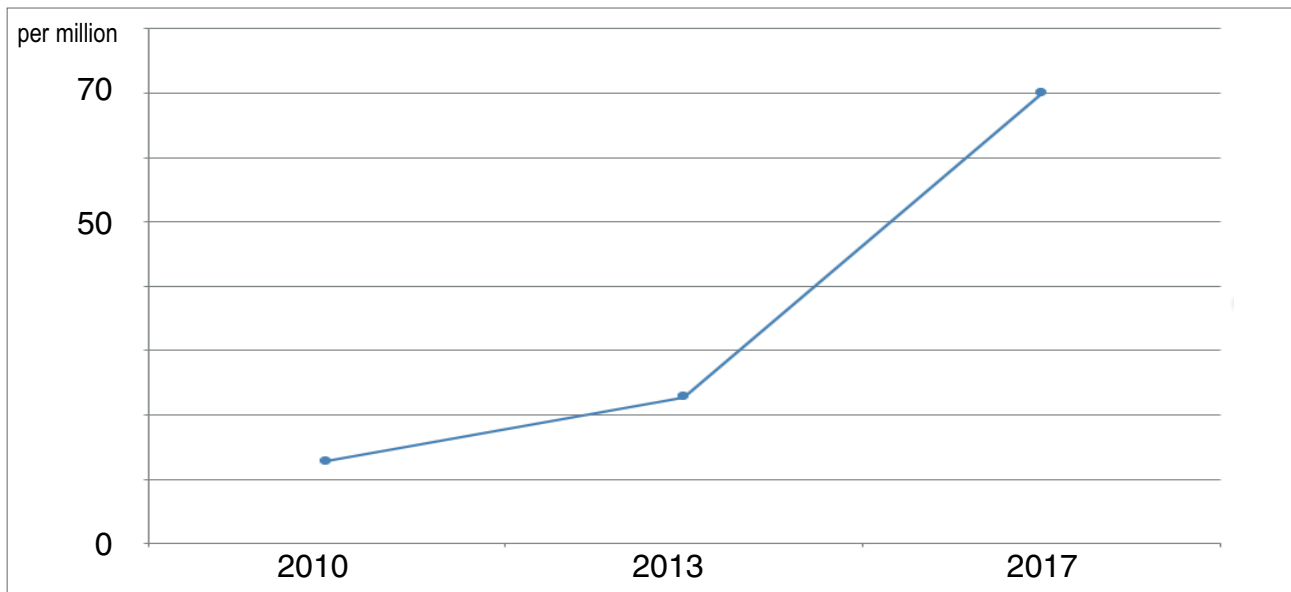


Figure 1. Temporal trend of cardiac ablation procedures per million of Lebanese

DISCUSSION

This study fills an unmet need and fills the gap of providing recent data on cardiac ablations in Lebanon. The 2017 EHRA White Book was published with CIED data on ESC member countries with no data on Lebanon. Lebanon, an ESC member country did not have data in the 2017 EHRA White Book [1]. Hence, there was an unmet need to have CIED data estimate in Lebanon. Our study shows a rise in cardiac ablations in Lebanon since 2010.

According to Refaat *et al.*, 50 to 60 ablation procedures were performed on average annually in Lebanon in 2010 [2]. Cardiac ablations increased to around 100 in 2013 [3]. Most of those performed cases are supraventricular tachycardias (atrioventricular nodal reentrant tachycardia and atrioventricular reentrant tachycardia including Wolff-Parkinson-White syndrome). Since 2010 and up to 2017, there has been a surge in catheter ablation procedures reaching around 70 per million Lebanese in 2017. The cardiac ablation procedures have increased over the last several years in Lebanon along with the number of cardiac electrophysiologists to around 20 [4].

There are several challenges to the development of electrophysiology in Lebanon. Most notably is the absence of a national perspective and governmental policies to improve the practice in Lebanon. Another major hurdle that faces the growth of the field in Lebanon is the issue of reimbursement. Around 75% of the population is covered by public insurance, 10% by private insurance, and 15% are not insured. Some of the electrophysiology catheters are not reimbursed.

Finally, there is an issue of public awareness regard-

ing cardiac ablations which the Lebanese Society of Cardiology Electrophysiology and Pacing Working Group tried to address. There is a need to have a national cardiac ablation registry.

This study has a limitation which is lack of capture of cardiac ablation procedures that did not have company support.

CONCLUSIONS

Cardiac ablation procedures have increased over the last several years in Lebanon in parallel with the number of cardiac electrophysiologists. It is important to have a national registry of cardiac ablations in Lebanon which will require financial support for its maintenance.

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CARDIAC ARRHYTHMIAS

EPIDEMIOLOGY OF ATRIAL FIBRILLATION FROM A DEVELOPING COUNTRY

Data from Lebanon AUBMC AF Registry

<http://www.lebanesemedicaljournal.org/articles/67-1/original3.pdf>

Mohammad SABRA¹, Bernard ABI-SALEH¹, Bernard HARBIEH¹, Maurice KHOURY¹, Marwan M. REFAAT^{1*}

Sabra M, Abi-Saleh B, Harbieh B, Khoury M, Refaat MM. Epidemiology of atrial fibrillation from a developing country: Data from Lebanon AUBMC AF Registry. *J Med Liban* 2019; 67 (1) : 10-14.

Sabra M, Abi-Saleh B, Harbieh B, Khoury M, Refaat MM. Épidémiologie de la fibrillation auriculaire dans un pays en voie de développement. Données du Centre médical de l'Université américaine de Beyrouth. *J Med Liban* 2019; 67 (1) : 10-14.

ABSTRACT • Objectives: In Lebanon, there are no updated data regarding the prevalence, incidence, and economic burden of atrial fibrillation population. We report our single center experience on the epidemiology of AF at the American University of Beirut Medical Center. **Methods:** We started the collection of data on patients with atrial fibrillation presenting at the American University of Beirut Medical Center [AUBMC] (Beirut, Lebanon) in 2015. **Results:** From 2015 to 2017, 103 patients with AF were included in the AUBMC AF Registry (57% men, 92% non-valvular etiology, 60% paroxysmal/25% persistent, 30% with coronary artery disease, 28% with diabetes, 72% with hypertension, 20% with congestive heart failure and 19% smokers). Our data showed that a large proportion of our patient population had a CHADS₂ and CHA₂DS₂-VASc scores greater than 2 and a significant proportion of patients with atrial fibrillation whose CHADS₂ and CHA₂DS₂-VaSc scores greater than 2 were not being treated with oral anticoagulation (OAC). Among patients on different OAC for stroke prevention, 32% are treated with vitamin K antagonist, 20% with dabigatran, 9% with apixaban, and around 39% with rivaroxaban. **Conclusion:** We describe our single center experience in developing an AF registry. There is a need for developing a national registry for patients with atrial fibrillation. This will help decision makers in assessing the needs of the population and intervening when necessary. Also, this could be helpful in improving AF research in Lebanon.

Keywords : atrial fibrillation; epidemiology; Lebanon

RÉSUMÉ • Objectifs: Au Liban, il n'existe pas de données actualisées concernant la prévalence, l'incidence et le fardeau économique de la population souffrant de fibrillation auriculaire (FA). Nous rapportons notre expérience sur l'épidémiologie de la FA au Centre médical de l'Université américaine de Beyrouth. **Méthodes:** Nous avons commencé la collecte de données de patients atteints de FA se présentant au Centre médical de l'Université américaine de Beyrouth [AUBMC] (Beyrouth, Liban) en 2015. **Résultats:** De 2015 à 2017, 103 patients AF ont été inclus dans le registre (hommes 57%; étiologie non valvulaire 92%; patients: paroxystiques 60%/25% persistants; maladie coronarienne 30%; diabétiques 28%; souffrant d'hypertension 72%; souffrant d'insuffisance cardiaque congestive 20%; fumeurs 19%). Nos données ont montré qu'une grande proportion de notre population de patients avaient des scores CHADS₂ et CHA₂DS₂-VASc > 2 et qu'une proportion significative de patients atteints de fibrillation auriculaire avec des scores CHADS₂ et CHA₂DS₂-VaSc > à 2 n'avaient pas été traités par anticoagulation orale. Parmi les patients traités par une anticoagulation orale pour accident vasculaire cérébral (AVC), 32% sont traités par antagoniste de la vitamine K, 20% par le dabigatran, 9% par l'apixaban et environ 39% par le rivaroxaban. **Conclusion:** Nous décrivons l'expérience de notre centre dans le développement d'un registre AF. Il est nécessaire de développer un registre national pour les patients atteints de fibrillation auriculaire. Cela aidera les décideurs à évaluer les besoins de la population et à intervenir si nécessaire. De plus, cela pourrait être utile pour améliorer la recherche sur la FA au Liban.

Mots-clés : fibrillation auriculaire; épidémiologie; Liban

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in adults worldwide. Atrial fibrillation is associated with an increased morbidity and mortality through causing and increasing risk of stroke and heart failure [1,2]. The implication of atrial fibrillation on the modern health care system continues to increase, mainly due to the

advancements in medical field that lead to an ever increasing ageing population. Atrial fibrillation is currently thought of as a significant public health concern.

Atrial fibrillation is currently the most common clinically significant dysrhythmia worldwide. The prevalence of atrial fibrillation was recently estimated at a worldwide occurrence of up to 33.5 million patients and affecting 2.5% to 3.5% of populations across the globe. In addition, the incidence of atrial fibrillation in developed countries was twice that in developing countries. [3].

This condition is also associated with an expected projected rise in incidence in the coming years where a total of 5.2 million people are expected to develop atrial fibril-

¹Department of Internal Medicine, Division of Cardiology, American University of Beirut Medical Center, Beirut, Lebanon.

*Corresponding author: *Marwan M. Refaat, MD*

e-mail: mr48@aub.edu.lb OR

marwanrefaat@alumni.harvard.edu

lation in the United States. This number is also forecasted to increase to 12.1 million over the coming 1-2 decades.

In Lebanon, there are no updated data regarding the prevalence, incidence, and economic burden of atrial fibrillation population. We report our single center experience on the epidemiology of AF at the American University of Beirut Medical Center.

METHODS

We started the collection of data on patients with atrial fibrillation presenting at the American University of Beirut Medical Center [AUBMC] (Beirut, Lebanon) in

2015. Data on the epidemiology of AF was reported for patients included in the AUBMC AF Registry between 2015 and 2017.

RESULTS

One hundred and three patients with AF were included in the AUBMC AF Registry (57% men, 92% non-valvular etiology, 60% paroxysmal/25% persistent, 30% with coronary artery disease, 28% with diabetes, 72% with hypertension, 20% with congestive heart failure and 19% smokers). Detailed demographics, AF characteristics, AF treatment, stroke risk and prevention as well as other medical conditions are summarized in Table I.

TABLE I PATIENT CHARACTERISTICS OF AUBMC ATRIAL FIBRILLATION (AF) REGISTRY

		N = 103	
Patient Characteristics		Number	Percentage
Demographics			
Age, y, %	< 65	34	33%
	65-74	39	37.8%
	> 75	30	29.2%
Male, %		59	57.3%
Race/Ethnicity, %	White	103	100%
AF Characteristics			
AF type, %	Non-valvular	95	92.2%
	Valvular	8	7.8%
AF duration, %	First detected	6	5.82%
	Paroxysmal	62	60.19%
	Persistent	26	25.24%
	Permanent	7	6.79%
	Unknown	2	1.94%
AF Treatment			
Rhythm control, %	Antiarrhythmic drug	49	47.57%
	Ablation	8	7.76%
Rate control, %		90	87.37%
Stroke risk and prevention			
CHADS ₂ score, median, IQR		2.0 (1.0-3.0)	
CHA ₂ DS ₂ -VASc score, median, IQR		2.0 (2.0-4.0)	
OAC among those with either CHADS ₂ or CHA ₂ DS ₂ -VASc score > 1, %	Acenocoumarol	25	24.27%
	Dabigatran	14	13.59%
	Rivaroxaban	30	29.12%
	Apixaban	7	6.79%
	Edoxaban	0	0%
Other medical conditions			
Coronary artery disease, %		31	30.1%
Diabetes, %		29	28.15%
Hypertension, %		74	71.84%
Current smoker		20	19.41%
Peripheral arterial disease, %		2	1.95%
Prior TIA/Stroke, %		10	9.70%
Congestive heart failure, %		21	20.28%
Chronic kidney disease, %	Stage IIIa (GFR 45-59)	11	10.67%
	Stage IIIb (GFR 30-44)	9	8.73%
	Stage IV (GFR 15-29)	0	0%
	Stage V (GFR < 15) or HD	1	0.97%

The distribution of AF patients by CHADS₂ and CHA₂DS₂-VASc scores are detailed in Figures 1a and 1b respectively. Our data showed that a large proportion of our patient population had a CHADS₂ and CHA₂DS₂-VASc scores greater than 2.

Furthermore, the prevalence of any oral anticoagulant (OAC) for stroke prevention across spectrum of CHADS₂ and CHA₂DS₂-VASc scores are detailed in Figures 2a and 2b respectively. It is clearly shown in those results that there is a significant proportion of patients with atrial fibrillation whose CHADS₂ and CHA₂DS₂-VASc scores are greater than 2 and who are not being treated with oral anticoagulation.

Moreover, Figure 3 shows the proportion of patients on different OAC for stroke prevention in the AUBMC registry. The figure shows that around 32% are treated with vitamin K antagonist (VKA), 20% with dabigatran, 9% with apixaban, and around 39% with rivaroxaban.

DISCUSSION

Stroke and systemic embolism are the most dreaded complications of atrial fibrillation since they carry increased morbidity and mortality. In fact, atrial fibrillation increases the risk of stroke around five times. Valvular atrial fibrillation increases the risk of stroke 20 times compared to patients with non-valvular atrial fibrillation [4]. Patients with documented atrial fibrillation are risk stratified according to their stroke risk and bleeding risk and a decision on their therapy is made. The most widely used tools are the CHA₂DS₂-VASc score for the stroke risk and the HASBLED score for the bleeding risk. A CHA₂DS₂-VASc score more than or equal to 2 requires oral anticoagulation according to most atrial fibrillation guidelines. Patients with moderate risk (CHA₂DS₂-VASc score = 1) can take antiplatelet therapy, but experts prefer anticoagulation.

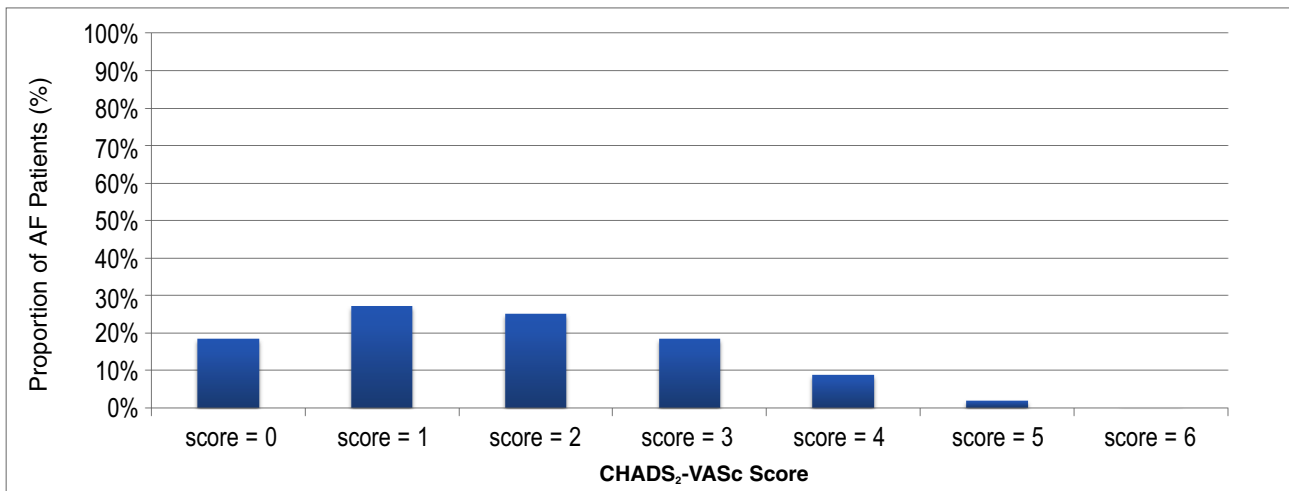


Figure 1a. Distribution of all AF patients CHADS₂ Scores

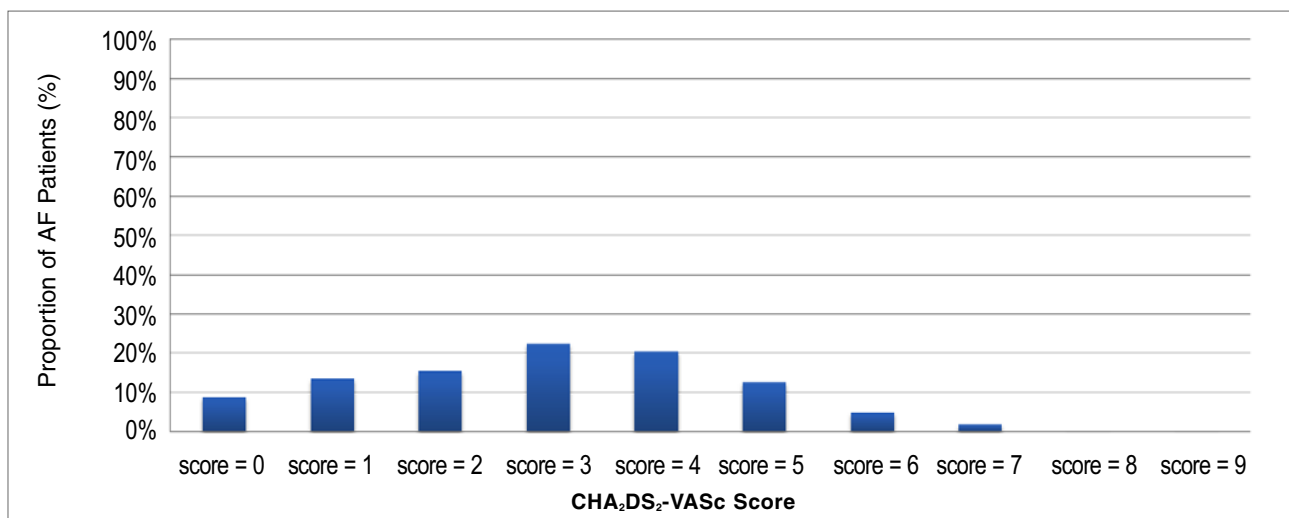


Figure 1b. Distribution of all AF patients CHA₂DS₂-VASc Scores

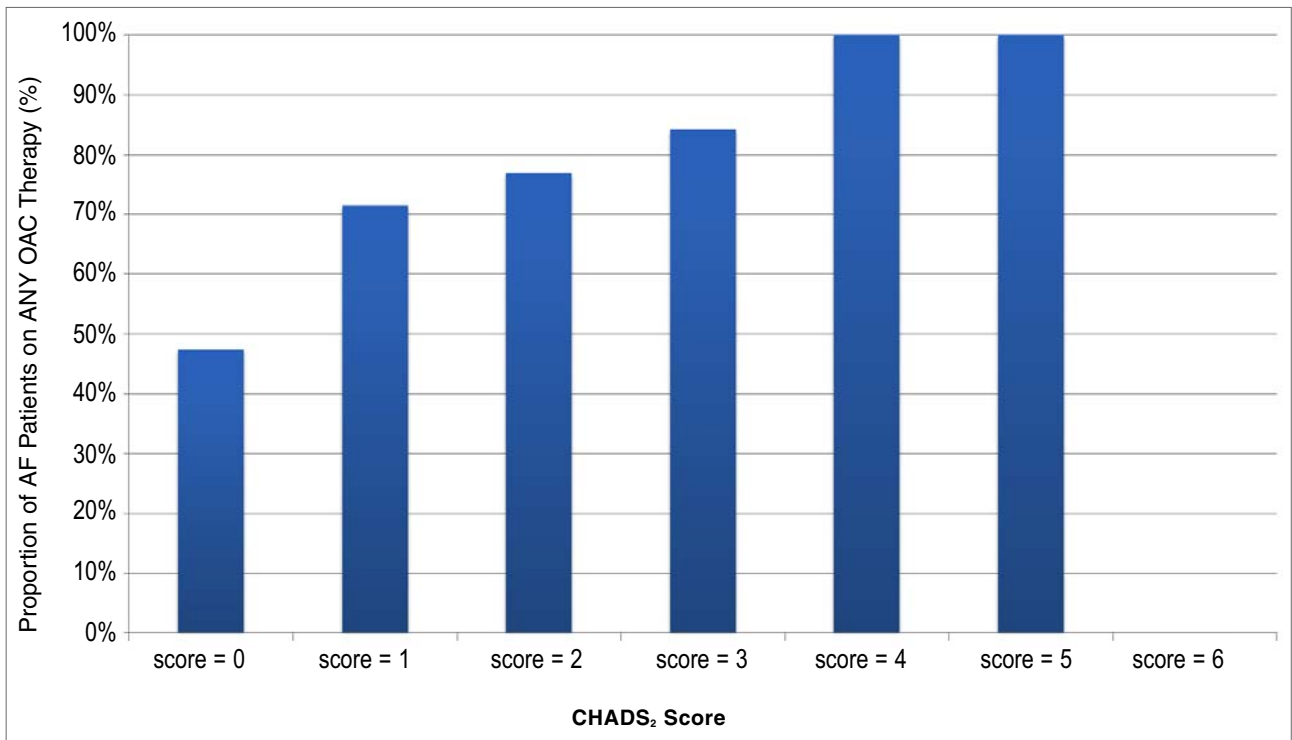


Figure 2a. Prevalence of any oral anticoagulant therapy across spectrum of CHADS₂ Scores

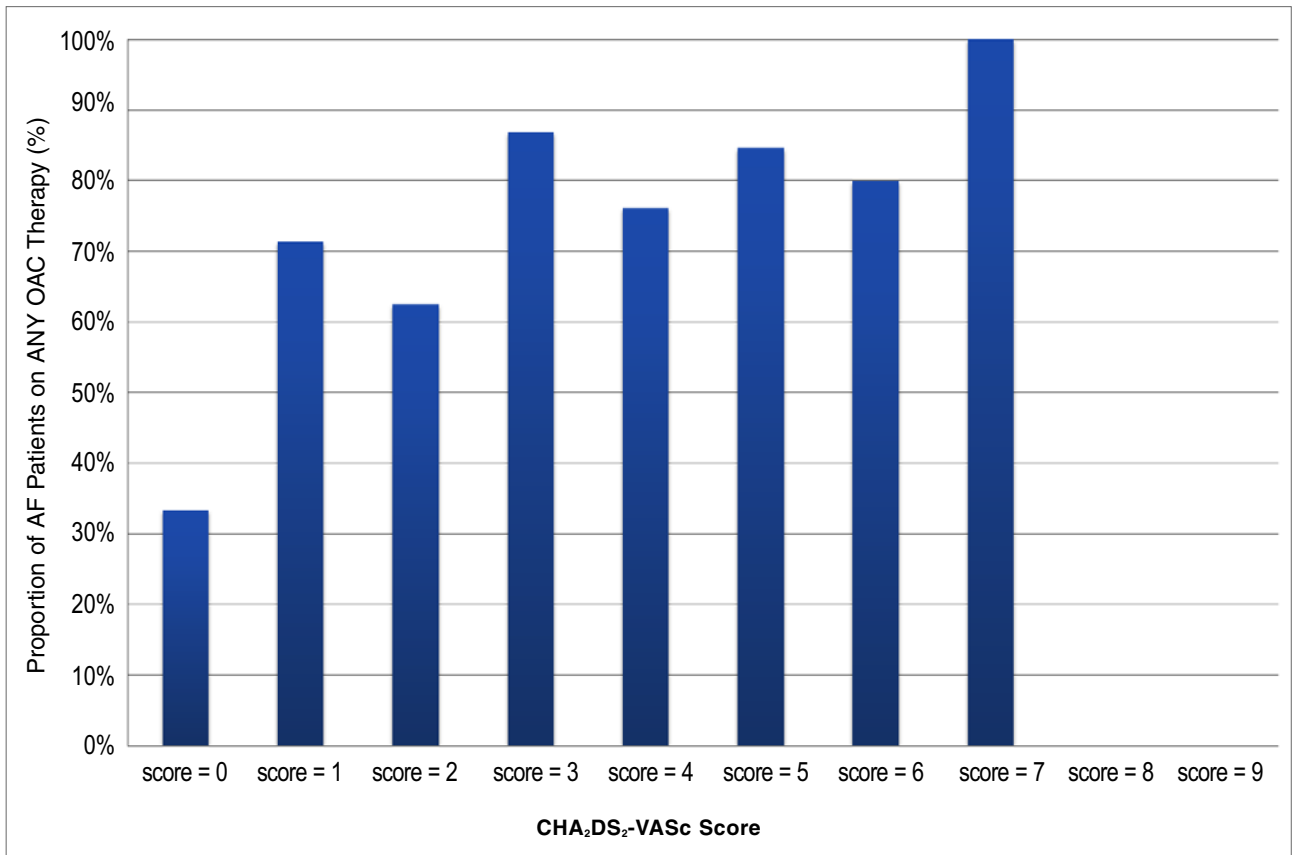


Figure 2b. Prevalence of any oral anticoagulant (OAC) therapy across spectrum of CHA₂DS₂-VASc Scores

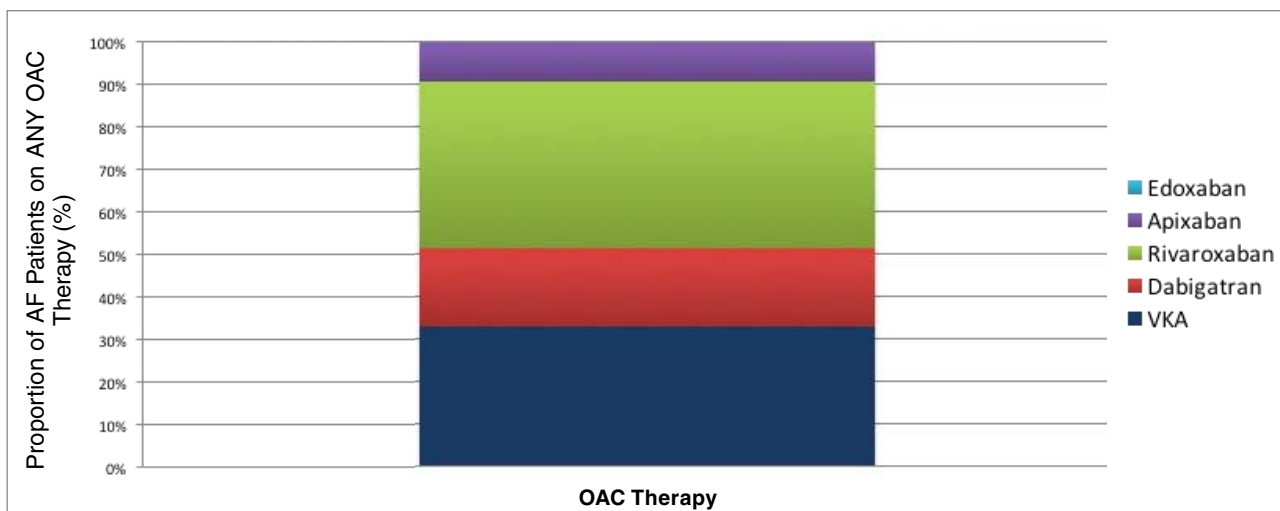


Figure 3. Prevalence of treatment strategies in all AF patients on OAC therapy

For those with low risk (CHA₂DS₂-VASc score = 0) antithrombotic therapy is not recommended [5].

Our data showed that a large proportion of our patient population had a CHADS₂ and CHA₂DS-VASc scores greater than 2. Hence, a large proportion of the population requires oral anticoagulation. Those results add another layer of complexity to the status of atrial fibrillation in Lebanon where a lot of our patients require prevention against strokes. This requires a national effort to raise awareness, improve diagnostics, and probably subsidize anticoagulants for those who can't afford them since the future social and economic burden of the complication of atrial fibrillation outweigh the present cost.

Furthermore, we found that a significant proportion of patients with atrial fibrillation whose CHADS₂ and CHA₂DS₂-VaSc scores are greater than 2 are not being treated with oral anticoagulation. Those data present an additional evidence to the need of awareness campaigns on stroke prevention in the setting of atrial fibrillation.

Our data shows that rivaroxaban was the most common OAC used. The choice of the most suitable OAC is subject to several considerations. Even though warfarin is efficient in reducing stroke from atrial fibrillation, it has numerous limitations that include: need for frequent monitoring of the international normalized ratio (INR), numerous drug-drug interactions, and dietary restrictions.

Furthermore, a new focused update to atrial fibrillation management guidelines from several North American societies explicitly prefers the latest generation of OAC over warfarin in stroke prevention [6]. Those new findings call for applying the latest standard of care as part of a national effort to reduce the social and economic burden of stroke due to atrial fibrillation.

CONCLUSIONS

We describe our single center experience in developing an AF registry. There is a need for developing a national registry for patient with atrial fibrillation. This will help decision makers in assessing the needs of the population and intervening when necessary. Also, this could be helpful in improving AF research in Lebanon.

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CARDIAC ARRHYTHMIAS

ROBOTIC REMOTE CATHETER NAVIGATION FOR ATRIAL FIBRILLATION ABLATION

A Single Center Experience

<http://www.lebanesemedicaljournal.org/articles/67-1/original4.pdf>

Marwan M. REFAAT¹, Mohamad K. SOUFI², John NOSBISCH², Alaa A. SHALABY^{2,3*}

Refaat MM, Soufi MK, Nosbisch J, Shalaby AA. Robotic remote catheter navigation for atrial fibrillation ablation: A single center experience. *J Med Liban* 2019; 67 (1) : 15-22.

Refaat MM, Soufi MK, Nosbisch J, Shalaby AA. Navigation robotique par cathéter à distance pour l'ablation de fibrillation auriculaire. Une étude monocentrique. *J Med Liban* 2019; 67 (1) : 15-22.

ABSTRACT • Objectives: There continues to be interest in use of robotic remote catheter navigation (RCN) in electrophysiology procedures. We describe our experience with RCN to perform radiofrequency ablation of atrial fibrillation (AF). **Methods:** We reviewed cases receiving RCN AF ablation and compared them to manual control navigation (MCN) procedures performed in the same time period by the same operator. Outcomes were followed through 24 months. **Results:** In a 2-year period, 70 and 45 patients received their initial RCN or MCN AF ablation, respectively. There were no significant differences in baseline clinical characteristics between patients receiving RCN or MCN. Among RCN patients, EF was lower and left atrial diameter larger in patients with persistent AF ($48.7 \pm 10.9\%$ and 52 ± 5 mm vs $55.2 \pm 6.6\%$ and 45 ± 10 mm, $p = 0.004$ and $p < 0.0001$, respectively). Total laboratory time was longer for RCN (380 ± 66 vs 350 ± 66.1 minutes, $p = 0.019$) while fluoroscopy time was shorter (20.7 ± 9.3 vs 24.8 ± 11.2 minutes, $p = 0.04$). Three patients in RCN group and none in the MCN group had postoperative complications ($p = 0.28$). By the end of two-year follow-up patients who received RCN were more likely to be free from AF (54 [70%] vs 22 [47%], $p = 0.002$). There was a trend toward increased utilization of atrioventricular node ablation among MCN patients (4 [9%] vs 1 [1%], $p = 0.06$). **Conclusions:** RCN AF ablation was associated with increased laboratory and ablation times but decreased fluoroscopy times. RCN was associated with higher rates of sinus rhythm maintenance at 24 months.

Keywords : atrial fibrillation; robotic; catheter ablation

ABBREVIATIONS

3D: three dimensional **AF:** atrial fibrillation
AAD: antiarrhythmic drugs **ICE:** intracardiac echocardiography

INTRODUCTION

Ablation therapy for atrial fibrillation has been demonstrated to be effective in controlling symptoms and reducing overall atrial fibrillation burden, with or without additional use of antiarrhythmic drugs [1,2]. Several factors impact the outcome of atrial fibrillation ablation

RÉSUMÉ • Objectifs: L'utilisation de systèmes de navigation robotique par cathéter à distance (RCN) dans les procédures électrophysiologiques continue de susciter de l'intérêt. Nous décrivons notre expérience avec RCN pour effectuer l'ablation par radiofréquence de la fibrillation auriculaire (FA). **Méthodes:** Nous avons examiné les cas pour lesquels une ablation de la FA par RCN était utilisée et les avons comparés aux procédures de navigation à contrôle manuel (MCN) effectuées au cours de la même période par le même opérateur. Les résultats ont été suivis pendant 24 mois. **Résultats:** Sur une période de 2 ans, 70 et 45 patients ont reçu leur première FA ablation par RCN ou MCN, respectivement. Il n'y avait pas de différences significatives dans les caractéristiques cliniques de base entre les deux catégories. Parmi les patients RCN, la fraction d'éjection était inférieure et le diamètre auriculaire gauche plus grand chez les patients atteints de FA persistante ($48,7 \pm 10,9\%$ et 52 ± 5 mm vs $55,2 \pm 6,6\%$ et 45 ± 10 mm, $p = 0,004$ et $p < 0,0001$, respectivement). Le temps total en laboratoire était plus long pour la RCN (380 ± 66 vs $350 \pm 66,1$ min, $p = 0,019$), tandis que le temps de fluoroscopie était plus court ($20,7 \pm 9,3$ vs $24,8 \pm 11,2$ min, $p = 0,04$). Trois patients du groupe RCN et aucun du groupe MCN ont présenté des complications post-opératoires ($p = 0,28$). À la fin du suivi de deux ans, les patients sous RCN étaient plus susceptibles de ne pas être atteints de FA (54 [70%] vs 22 [47%], $p = 0,002$). Il y avait une tendance à l'utilisation de l'ablation du nœud auriculo-ventriculaire chez les patients traités par MCN (4 [9%] vs 1 [1%], $p = 0,06$). **Conclusions:** L'ablation de la FA par RCN était associée à une augmentation des temps de laboratoire et d'ablation, mais à une réduction du temps de fluoroscopie. La RCN était associée à des taux plus élevés de maintien du rythme sinusal à 24 mois.

Mots-clés : fibrillation auriculaire; robotique; ablation par cathéter

including left atrial size, duration and nature of atrial fibrillation (paroxysmal versus persistent) as well as comorbid conditions [1-7].

Ablation strategies for atrial fibrillation have evolved over time. It is now widely accepted that complete isola-

¹Section of Cardiac Electrophysiology, Division of Cardiology, American University of Beirut Medical Center, Beirut, Lebanon.

²Division of Cardiology, VA Pittsburgh Healthcare System and ³Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA.

*Corresponding author: Alaa A. Shalaby, MD.

e-mail: Alaa.Shalaby@va.gov OR imbolus@yahoo.com

tion of the pulmonary veins with demonstration of entrance and exit block are the mainstay of ablative therapy. In the case of persistent atrial fibrillation connecting lines between isolated antra and adjacent anatomic barriers and critical atrial structures have been employed [7-9]. With this strategy ablation of persistent AF remains a complex undertaking that requires lengthy intervention with the potential for prolonged fluoroscopic exposure to the patient and cumulatively to the operator [8-11]. In addition, prolonged standing or sitting in the fluoroscopy suite with protective lead aprons poses a potential health hazard to operators who are subjected to stresses on the spine of the back and neck as they operate catheters while integrating multiple visual inputs from EP and hemodynamic monitoring and recording systems, fluoroscopy, and non-fluoroscopic navigational systems [12].

Robotic remote catheter navigation (RCN) has been a topic of interest in clinical cardiac electrophysiology [13-19]. In addition to removing the operator from the immediate fluoroscopy environment, RCN offers the promise of better catheter stability and possibly greater lesion efficacy [20-21]. However, there has been little outcome data from clinical trials or real world experience. In this report, we describe our single center experience incorporating RCN into routine use for atrial fibrillation ablation. Furthermore, we assess two-year outcome among patients receiving initial ablation therapy guided by either RCN or MCN.

METHODS

Patients

Patients receiving their initial ablation procedure for symptomatic atrial fibrillation at the VA Pittsburgh Healthcare System electrophysiology laboratory over a two-year period were reviewed. These were patients for whom a rhythm control strategy had been decided and who had failed at least one antiarrhythmic drug.

All cases were considered for use of the robotic system. MCN was chosen at the discretion of the operator mainly due to laboratory time constraints or other logistical reasons such as availability of catheters at the time of the procedure. Data were retrospectively obtained from the electronic medical record with the following variables specifically charted: procedure time, fluoroscopy time and ablation time, in addition to patient demographics and clinical characteristics.

Follow-up procedures and maintenance of sinus rhythm were assessed for two years for all patients. VA Pittsburgh Healthcare System IRB approval was obtained to conduct this review.

Ablation procedure

In all patients a CT scan with 3D reconstruction was performed prior to the procedure. For all cases, manual and robotic, procedure time started with entry into the electrophysiology laboratory and included intubation for general anesthesia, a transesophageal echocardiogram, placement of an esophageal temperature probe as well as femoral venous and arterial sheath placement and removal after reversal of heparinization with protamine. Fluoroscopy time was recorded by the fluoroscopy system and documented in the chart.

Robotic procedure

The robotic system (Sensei Robotic Catheter System, Hansen Medical, Mountain View, CA, USA) has been previously described. In summary, a workstation placed at a remote location from the patient's table includes the motion controller which allows the physician to manipulate the catheter remotely. Robotic navigation of the sheath and catheter ensemble is possible within fluoroscopic, ICE or electroanatomic mapping images.

All patients were anticoagulated with warfarin prior to the procedure with at least 3 weekly therapeutic INR levels [2-3]. Patients underwent the procedure with therapeutic INR on the morning of the procedure. Femoral venous access was obtained in the right and left groins. The left femoral vein access involved a 14F long sheath to allow passage of the robotic sheath. Two sheaths (SR0 9F and Agilis 8.5F, St. Jude Medical, St Paul, MN, USA) were inserted to allow use of radial intracardiac echocardiography (ICE, UltraIce, Boston Scientific, Natick, MA, USA) from the right atrium first to guide transeptal puncture through the fossa ovalis. After transeptal puncture, ICE imaging of the left atrium was accomplished with the deflectable Agilis sheath. Prior to transeptal puncture, heparin was initiated to achieve and maintain an activated clotting time above 300 sec.

Using a multipolar catheter, an electroanatomic map of the left atrial chamber anatomy was reconstructed (EnSite NavX system, St. Jude Medical, St Paul, MN, USA). Once formed the 3D image was fused with the 3D CT image imported into the mapping system. The transeptal crossing point was tagged in the 3D image. After the transeptal sheath was withdrawn into the right atrium the robotic sheath with the ablation catheter was robotically manipulated under visualization by fluoroscopy, ICE and electroanatomic image to cross the preformed transeptal passage and directed to the left pulmonary vein vestibule (Cf. video). The deflectable sheath (Agilis) was then manually reinserted into the left atrium to allow imaging with the ICE catheter. All ablation lesions were delivered under direct real time visualization with ICE imaging. Pulmonary vein antrum isolation was per-

formed with a 3.5-mm irrigated catheter (Biosense Webster, Diamond Bar CA, USA) with target settings of 30 watts, 35°C. After the complete lesion set encircling the antrum was delivered, electrograms were explored at a deeper level and in the carina region of the respective vestibule and secondary lesions were delivered as necessary. Using a multipolar spiral catheter entrance block was confirmed. In sinus rhythm pacing from within each vein with the same spiral catheter was then performed to confirm exit block.

In all cases of persistent atrial fibrillation a 20 pole catheter was placed through a separate venous access sheath to straddle the right atrium free wall sweep caudally and enter as deep as possible in the coronary sinus. When ablating in the right atrium, the multipolar spiral catheter was placed in the superior vena cava (SVC) to assess its isolation (Figure 1).

Persistent cases received lines in the following order with the endpoint of conversion to sinus rhythm or a pace-terminable regular atrial tachycardia: A. Within the left atrium: 1) Along the roof (between the cranial extents of the two isolation lines around ipsilateral veins; 2) Along the floor between the caudal extents of the two isolation circles around ipsilateral veins and parallel to the coronary sinus catheter; 3) Along the septum anterior to the circle isolating the right pulmonary veins to the fossa ovalis and 4) A lateral mitral isthmus between the lateral end of the mitral isthmus to the caudal portion of the circle isolating the left veins. B. If after these lines sinus rhythm or atrial tachycardia had not been achieved, the robotic sheath and ICE catheter were withdrawn to the right atrium and lesions were delivered within the coronary sinus (Figure 1), to isolate the superior vena cava and along the crista terminalis guided by registered

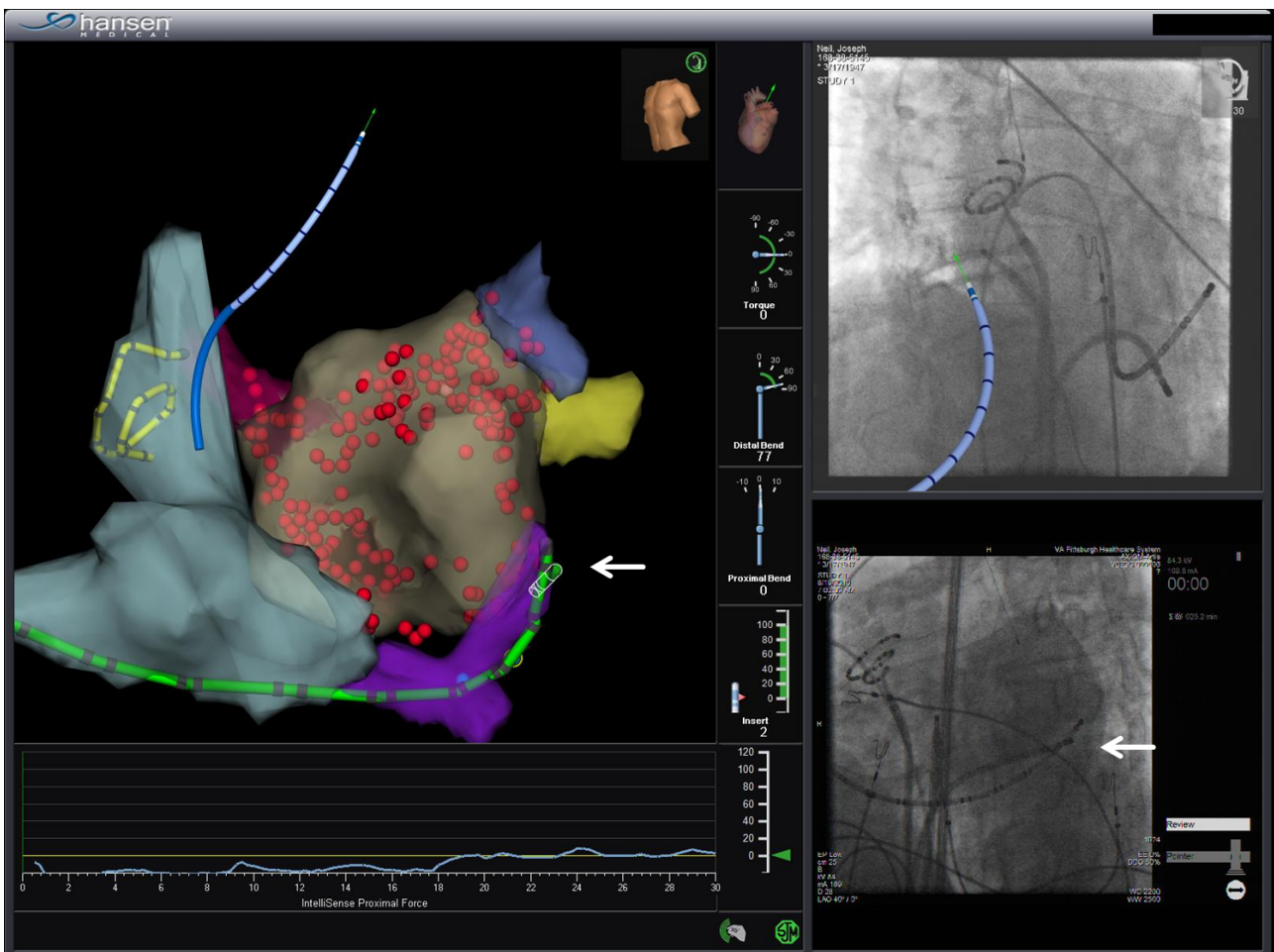


Figure 1. Screen shot of the Robotic console during a persistent AF ablation

The main screen shows the electroanatomic map with diagnostic catheters in the right atrium, coronary sinus and SVC. A virtual representation of the 3D orientation of the robotic sheath in real time is shown. Also shown are the fluoroscopic views in RAO and LAO. The tip of the ablation catheter within the robotic sheath is shown in the coronary sinus (electroanatomic map and LAO fluoroscopy, ←). The feed from the ICE display can be exchanged for any one of these displays. At the side are representations of the different moves of the robotic sheath. At the bottom of the screen is the display of the friction forces over time. See text for details.

atrial electrograms from those regions. High output pacing to ensure there was no phrenic nerve capture was performed by the ablation catheter prior to radio frequency (RF) energy delivery. The endpoint was to restore sinus rhythm.

If not achieved with ablation, overdrive pacing of an organized atrial tachycardia if present was performed. Otherwise direct current cardioversion at the end of the procedure restored sinus rhythm. After sinus rhythm had been restored, all pulmonary veins were revisited with manual manipulation of a spiral catheter pacing from within the vestibules to confirm exit block.

Manual procedure

The same technique and tools were employed other than the robotic arm for paroxysmal or persistent AF. Double transeptal puncture was performed with a fixed curve transeptal sheath to deliver the ablation catheter (SL1, St. Jude Medical) while left atrial ICE imaging was accomplished with a deflectable sheath (Agilis).

Follow-up

Auto-triggered event recording for thirty days was used in all patients to monitor events during the first month and whenever needed to evaluate recurrent symptoms. Follow-up was conducted at 3 and 6 months and at 6 monthly intervals thereafter. In addition to history and physical, Holter monitoring or thirty-day event monitor was repeated as needed. Patients with persistent recurrences of atrial fibrillation or flutter underwent cardioversion after the first month [had passed]. Antiarrhythmic drugs were prescribed as needed. All patients were instructed to continue anticoagulation. Follow-up data

through 24 months, available on all patients, were reviewed for the purpose of this report.

Statistical analysis

Continuous data are represented as mean \pm standard deviation. The two-tailed Student's t-test was used for comparing continuous unpaired samples, assuming unequal variances. Mann-Whitney U non-parametric test was used for comparing continuous variables that are not normally distributed. For categorical variables Fisher's exact test was performed. Two-sided *p* values < 0.05 were considered statistically significant.

Statistical calculations were performed using SPSS13 (SPSS Inc, Chicago, IL, USA).

RESULTS

Baseline characteristics

Between January 2009 and December 2012 a total of 115 consecutive first time ablation procedures were performed by the same operator. Of these 70 were RCN cases. These were equally divided among paroxysmal and persistent cases. Table I describes the cohort; patients were generally older and predominantly Caucasian males. There was no difference in clinical characteristics between the two groups. Table II further describes the RCN group according to the presenting arrhythmia. Significant differences within the RCN group between persistent and paroxysmal patients were present for ejection fraction (EF) (43.4 ± 6.2 vs 50.3 ± 7.3 , $p < 0.0001$) and left atrial diameter (55.2 mm ± 6.6 mm vs 48.7 mm ± 10.9 mm, $p = 0.004$) reflective of advanced disease among patients with persistent AF.

TABLE I
CHARACTERISTICS OF THE STUDY COHORT
ACCORDING TO ABLATION METHOD

Baseline characteristics	RCN (N = 70)	MCN (N = 45)	<i>p</i> Value
Male (%)	69 (99)	42 (93)	0.30
Age (yrs)	63 \pm 6.5	63.8 \pm 6.3	0.52
Caucasians (%)	66 (94)	43 (93)	1.0
Paroxysmal atrial fibrillation (%)	35 (50)	29 (64)	0.18
Hypertension (%)	63 (90)	42 (93)	0.73
Coronary artery disease (%)	20 (29)	11 (24)	0.63
DM	30 (43)	17 (38)	0.69
Prior CVA	5 (7)	2 (4)	0.70
BMI	35.1 \pm 11.1	32.8 \pm 5.5	0.20
Left atrial diameter (mm)	47 \pm 7.6	46.9 \pm 6.6	0.77
Ejection fraction (%)	52 \pm 9.5	52 \pm 11	0.99

RCN: robotic controlled navigation MCN: manually controlled navigation
DM: diabetes mellitus CVA: cerebrovascular accident BMI: body mass index

TABLE II
CLINICAL CHARACTERISTICS OF RCN GROUP
ACCORDING TO UNDERLYING ATRIAL FIBRILLATION

Baseline characteristics	Paroxysmal (N= 35)	Persistent (N= 35)	<i>p</i> Value
Male (%)	35 (100)	34 (97)	1.0
Age, yrs, mean \pm SD	62 \pm 7.1	64.1 \pm 5.8	0.18
Caucasians (%)	32 (91)	34 (97)	0.61
Hypertension (%)	26 (74)	27 (77)	1.0
Coronary artery disease (%)	9 (26)	11 (31)	0.79
DM	13 (37)	17 (49)	0.46
PVD	0 (0)	2 (6)	0.49
Prior CVA	2 (6)	3 (9)	1.0
BMI	33.4 \pm 7.8	34.4 \pm 4.2	0.51
Left atrial size (mm)	43.4 \pm 6.2	50.3 \pm 7.3	< 0.0001
Ejection fraction (%)	55.2 \pm 6.6	48.7 \pm 10.9	0.004

PVD: peripheral vascular disease CVA: cerebrovascular accident
BMI: body mass index DM: diabetes mellitus

TABLE III
PROCEDURAL AND MIDTERM OUTCOME AMONG PATIENTS TREATED WITH RCN OR MCN

Parameters	RCN (N = 70)	MCN (N = 45)	p-Value
Acute complete PVAI (%)	100	100	NS
Lab time (min)	380 ± 66	350 ± 66.1	0.019
Fluoroscopy time (min)	20.7 ± 9.3	24.8 ± 11.2	0.04
Ablation time (min)	71.5 ± 35.5	62.3 ± 24.3	0.14
Conversion of PER AF during ablation (%)	16/35 (46)	5/16 (31)	0.37
On antiarrhythmic therapy at 24 months (%)	38 (54)	21 (47)	0.45
DCCV within 24 months (%)	15 (21)	11 (24)	0.82
Repeat PVI ablation within 24 months (%)	8 (11)	3 (7)	0.53
Ablate and pace by 24 months (%)	1 (1)	4 (9)	0.06
Freedom from AF at 24 months (%)	54 (70)	22 (47)	0.002

RCN: robotic controlled navigation MCN: manually controlled navigation PVAI: pulmonary vein antral isolation
DCCV: direct current cardioversion

Procedural outcomes

Intracardiac echocardiography-guided circumferential pulmonary vein antral isolation (PVAI) using RCN integrated with NAVX electroanatomic mapping system was accomplished in all RCN cases. Acute complete PVAI, defined by entrance and exit block was achieved in all RCN and MCN patients.

Table III describes the procedural outcome of both RCN and MCN groups. Both ablation time (71.5 ± 35.5 min vs. 57.4 ± 23.3 min, $p = 0.02$) and overall laboratory time (370 ± 72 min vs. 325 ± 57 min, $p = 0.008$) were longer for RCN patients; however, this was associated with shorter fluoroscopy time (19.4 ± 8.5 min vs. 24.1 ± 7.7 min, $p = 0.02$).

Among RCN patients, when persistent and paroxysmal

patients were compared, laboratory time for persistent was significantly longer (417.2 ± 43.3 min vs. 343.1 ± 72.5 min, $p = 0.0002$), as was ablation time (95.3 ± 38.6 min vs. 52.5 ± 17.2 min, $p = 0.003$). This difference in times reflects the strategy employed at the time involving multiple lines with sinus rhythm restoration as a procedural endpoint. Fluoroscopy time, however, was not significantly different (17.9 ± 7.7 min vs. 20.9 ± 9.2 min, $p = 0.2$).

Laboratory time for RCN in both groups diminished in the first year with progressive case numbers. This reflects an expected learning curve effect with procedure time decreasing with a higher number of cases performed. Scatter plots charting the time variable against case number were fit with a simple linear regression model for each clinical scenario. Representative analyses in Figure 2 by

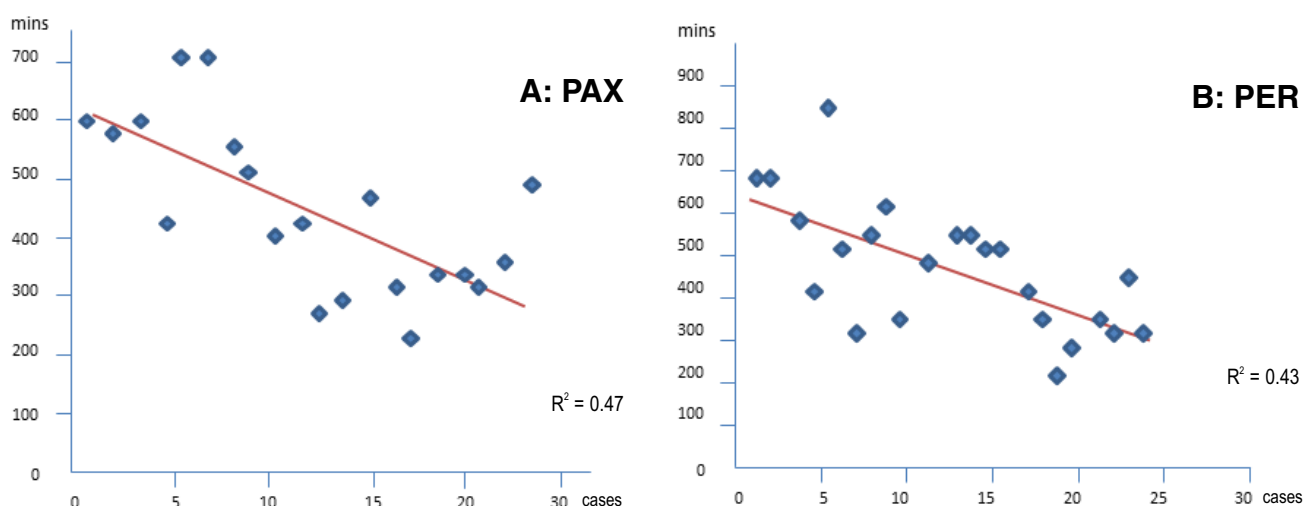


Figure 2. Scatter plots of procedure time vs case number among RCN treated patients (paroxysmal “PAX”: panel A and persistent “PER”: panel B) of RCN ablation cases. The negative slope of the linear regression model fit indicates shorter times with increasing cases reflective of the initial learning curve.

scatter plots of procedure time among the persistent group (panel A) and the paroxysmal group (panel B) show the decrease in procedure time with cases.

Although no single curve accurately represents the data, the time index decreased with experience as evidenced by the negative slope of the linear regression model fits (paroxysmal group: slope is -12.3 min/case, p value < 0.001; persistent group: slope is -14.6 min/case, p value < 0.001).

On univariate analysis, the number of cases done was inversely associated with procedural time for both patients with paroxysmal AF ($\beta = -12.25$, 95% CI [-18.4; -6.0], $p < 0.0001$) and persistent AF ($\beta = -14.6$, 95% CI [-22.2, -6.9], $p < 0.0001$).

Procedural and two-year outcome

There were no significant differences in procedural outcome and follow-up management between the groups (RCN vs. MCN, Table III). Recurrences in the first month were common in both groups. A notable proportion of patients remained on anti-arrhythmic drug therapy at last follow-up (38 [54%] vs. 21 [47%], $p = 0.45$). At the end of two years, there was a trend to increased utilization of ablate and pace among patients treated with MCN. Patients treated with RCN were significantly more likely to be free from AF at the end of two years (54 [70%] vs. 22 [47%], $p = 0.002$).

Complications

No complications were noted in the MCN group while 3 (3%) complications occurred in the RCN group ($p = 0.28$). A left thigh hematoma after a re-bleed from the site of the 14F sheath inserted in the left femoral vein occurred in an obese patient (no.7, BMI = 39.4) causing mild rhabdomyolysis (peak CPK 15,093 units; no resultant renal impairment) and transient femoral nerve palsy which fully recovered by 3 months. One patient (no. 10) exhibited right phrenic nerve palsy that had fully resolved after 8 months. We previously reported a patient (no. 22) presenting with fever and sepsis due to esophageo-pericardial fistula few weeks after ablation in whom conservative management was successful [22]. Specifically, no acute cardiac or vascular perforations or pericardial effusions were encountered. On follow-up, there was no evidence of patients developing pulmonary vein stenosis.

DISCUSSION

We report our initial experience and two-year follow-up on RCN ablation with concomitant real time ICE imaging. We found RCN to be equally effective as MCN in achieving pulmonary vein isolation acutely. This was achieved with longer laboratory times, however, which

tended to decrease with increasing case numbers reflective of an expected learning curve. Fluoroscopy times were shorter than those for MCN cases in face of overall longer ablation delivery. Compared to MCN, acute procedural and follow-up outcomes were favorable. Most importantly, a significantly higher proportion of RCN treated patients were free of AF at the end of two years.

As in previous reports, we found RCN, in our case deployed with continuous ICE and electroanatomic imaging, provided precise as well as stable positioning which potentially improved the efficacy of ablation lesions [20-22]. Our findings are in agreement with Ullah *et al.* who in a multicenter prospective registry found a higher one-year success rate with RCN combined with a catheter force sensor when compared with MCN historical controls. This advantage was not present when catheter force sensing was employed in MCN cases [23]. Because of the remote location of the workstation from the fluoroscopy, radiation exposure to the physician was reduced. This is particularly relevant as many of our patients were overweight or obese (Table I), a factor that increases radiation exposure to the operator. We also found that total fluoroscopy time was reduced and further decreased with increasing experience reflecting a decrease in radiation exposure to the patient as well. Rather than any inherent advantage for RCN, this is probably a result of the ability to navigate RCN in 3D space visualized by ICE, virtual electroanatomic mapping and fluoroscopy.

Persistent atrial fibrillation

Ablation procedures for persistent AF can be particularly challenging as they are usually associated with larger atria and impaired ejection fraction. In addition to PVI, linear and focal lesions are frequently applied to critical sites within the left and right atrium as well as the superior cava and coronary sinus [24]. We found RCN to be intuitive, with no difficulty in reaching desired target areas. We noted that ablation times were longer when using RCN particularly among persistent cases. This may reflect the ability to deliver such lengthy lesion sets with improved operator ergonomics, less fatigue and the operator's awareness of satisfactory shielding from radiation exposure. Longer ablation time reflecting larger lesion sets, alone, may have been responsible for the trend toward higher rates of acute conversion during the ablation procedure among PER cases presenting in AF; conversion itself being a positive prognostic factor [25]. Overall, as previously reported by others we observed a high level of catheter stability and tissue contact with RCN that may have also been responsible for the observed effect [19-21]. This favorable effect was durable as shown in the 2-year follow-up data. While continued

antiarrhythmic therapy and repeat interventions (cardioversion or ablation) were required [19], patients were more likely to maintain sinus rhythm after the index RCN ablation procedure.

Overall safety

The main concern with RCN is loss of tactile feedback. In this context, it is notable that there were no vascular or cardiac perforations in our series. The RCN system provides feedback on friction forces between the sheaths as a surrogate for pressure forces on a visual and tactile vibratory scale. In this report, we demonstrate the feasibility of using real time ICE as an added safety measure. Nevertheless, injury to contiguous extra-cardiac structures as we encountered, while not statistically significant, could be related to increased contact force [22]. An increased incidence of subclinical esophageal injury was previously reported with RCN [23]. Catheters with contact force sensors, not available at the time of this study, are currently approved (Biosense Webster, Boston, MA USA, St. Jude Medical, Minnetonka, MN USA) with reports of improved lesion delivery and safety.

Study limitations

Our study adds to a growing body of literature describing initial experience using RCN ablation and among the first to compare outcomes between RCN and MCN strategies. We believe our report is valuable as findings from sites like ours present real world experience applicable to the majority of ablation centers. We recognize that our study is a retrospective patient series study and the usual limitations to such chart review studies apply. In absence of randomization, confounding factors could influence the comparison to MCN to favor either arm. Our patient population, reflective of the VA population in general, comprised a large proportion of elderly Caucasian males. The safety and efficacy profile of RCN among women may be different. The laboratory times recorded in the chart and reported in the current study includes preparation time, sheath removal and other procedures that are not directly part of the ablation procedure itself (e.g. intubation/TEE) but are charted together with the specific ablation part of the procedure. Notwithstanding, it is apparent that procedure times are prolonged with use of RCN in part due to initial preparation time. Increased ablation times on the other hand may reflect operator comfort with RCN.

CONCLUSIONS

RCN is a promising technology that may have a role as a tool for atrial fibrillation ablation where it can decrease fluoroscopy time and fluoroscopy exposure significantly.

RCN may be particularly suited for persistent AF ablation. RCN adoption is associated with a learning curve such that procedure and fluoroscopy times decrease with increasing operator and facility experience. Complications with use of RCN need to be guarded against and monitored carefully, particularly early in the experience.

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CARDIAC ARRHYTHMIAS

EVOLUTION MECHANICAL DILATOR SHEATH AS A FIRST CHOICE FOR TRANSVENOUS LEAD EXTRACTION

<http://www.lebanesemedicaljournal.org/articles/67-1/original5.pdf>

Marwan M. REFAAT^{1*}, Rana COSTA^{1*}, Joseph I. WANG², Hadi SKOURI¹, Patrick LAHOUD³, Maurice KHOURY¹
Antoine B. ABCHÉE¹, Byron K. LEE^{2*}, Bernard ABI-SALEH^{1**}

Refaat MM, Costa R, Wang JI, Skouri H, Lahoud P, Khoury M, Abchée AB, Lee BK, Abi-Saleh B. Evolution mechanical dilator sheath as a first choice for transvenous lead extraction. J Med Liban 2019; 67 (1): 23-27.

Refaat MM, Costa R, Wang JI, Skouri H, Lahoud P, Khoury M, Abchée AB, Lee BK, Abi-Saleh B. La gaine de dilatation mécanique Evolution comme premier choix pour l'extraction des sondes intravasculaires. J Med Liban 2019; 67 (1): 23-27.

ABSTRACT • Objectives: The Evolution mechanical dilator sheath (Cook Medical) uses a rotational mechanism and a bladed tip to overcome fibrosis around cardiovascular implantable electronic devices (CIED) leads. There are only a few reported case series where the Evolution system was used as the first-line choice for CIED lead extraction. The purpose of this study was to report the success of the Evolution system as a first line tool in two centers: the University of California San Francisco Medical Center (San Francisco, CA, USA) and the American University of Beirut Medical Center (Beirut, Lebanon). **Method:** Between July 2011 and May 2015, the Evolution sheath was used for extraction of pacemaker or implantable cardioverter-defibrillator (ICD) leads in 43 patients (88 leads). Success and complications were defined according to the Heart Rhythm Society expert consensus document on lead extraction. **Results:** Indications for extraction were infection with or without bacteremia, lead malfunction and subclavian vein stenosis. Evolution was used as first choice in all patients, with 100% clinical success. Complete procedural success was achieved in 38 patients (88.3%); in five patients, the distal electrode with the distal end of the right atrial (RA) or right ventricular (RV) coil was retained. Adverse events were limited to one patient having a consequent pneumothorax and another having a pericardial effusion that did not cause any hemodynamic compromise. **Conclusion:** Our data suggest that the Evolution mechanical dilator sheath is a useful and safe tool to be used as first line management in transvenous lead extraction.

Keywords: defibrillation-ICD; pacing; extraction; Evolution system

RÉSUMÉ • Objectifs: La gaine de dilatation mécanique Evolution (Cook Medical) utilise un mécanisme de rotation et une pointe à lame pour surmonter la fibrose autour des dérivations d'appareils électroniques implantables cardiovasculaires (CIED). Il n'y a que quelques séries de cas rapportés pour lesquels le système Evolution a été utilisé comme premier choix pour l'extraction de CIED. L'objectif de cette étude est de rapporter le succès du système Evolution en tant qu'outil de première ligne dans deux centres: le centre médical de l'Université de Californie à San Francisco (San Francisco, Californie, États-Unis) et le centre médical de l'Université américaine de Beyrouth (Liban). **Méthodes:** Entre juillet 2011 et mai 2015, la gaine Evolution a été utilisée pour l'extraction des sondes de stimulateur cardiaque ou de défibrillateur automatique implantable (ICD) chez 43 patients (88 sondes). Le succès et les complications ont été définis selon le document de consensus des experts de la Heart Rhythm Society sur l'extraction. **Résultats:** Les indications pour les extractions étaient des infections avec ou sans bactériémie, dysfonctionnement de la sonde et sténose de la veine sous-clavière. La gaine Evolution a été utilisée comme 1^{er} choix chez tous les patients, avec un succès clinique de 100%. Le succès complet de la procédure a été atteint chez 38 patients (88,3%). Les événements indésirables ont été limités à un patient ayant un pneumothorax et un autre ayant un épanchement péricardique ne causant aucun trouble hémodynamique. **Conclusion:** Nos données suggèrent que la gaine de dilatation mécanique Evolution est un outil utile et sûr à utiliser comme traitement de première intention dans l'extraction transveineuse du CIED.

Mots-clés: défibrillateur; stimulateur cardiaque; extraction; système Evolution

INTRODUCTION

Since the implantation of the first pacemaker in 1958, it is estimated that more than 400,000 CIEDs, including implantable cardioverter defibrillators and permanent pacemakers, are currently implanted yearly in the United States [1,2]. As experience with CIEDs grew, more and

more clinical issues started to arise. Additionally, the increasing use of CIEDs, due to broader indications and improved cardiovascular outcomes, and the longer life expectancy of patients brought complicated procedures to the frontline [3]. During this time, everything from the insulation material placed on leads to the technique of insertion was questioned and studied in order to improve

¹Cardiac Electrophysiology Section/Cardiology Division, American University of Beirut Medical Center, Lebanon.

²Cardiac Electrophysiology Section/Cardiology Division, University of California San Francisco Medical Center, San Francisco, CA, USA.

³Cardiology Division, Hôpital Notre Dame de Secours, Lebanon.

*Equal contribution.

**Corresponding author: Bernard Abi-Saleh, MD.

e-mail: ba47@aub.edu.lb

the process of CIED implantation and to decrease the complications thereafter.

One of the largest hurdles tackled at that point was the safe removal of problematic CIEDs. In general, it was noticed that removal of the pulse generator system was relatively straight forward, as well as the removal of recently implanted leads. However, removal of chronically inserted leads rose as a challenge [3]. Chronic contact with venous and endocardial structures induces fibrosis and eventual calcification, making extraction a delicate and complicated procedure. Thus, the area of safe lead extraction developed quickly, mainly after 1988, to the point where it has become a specialized procedure with specific techniques and recommendations as well as improving results [3,4].

Many methods for lead extraction have been developed including manual traction, locking stylets, snares, mechanical sheaths, laser sheaths, electro-surgical sheaths and telescoping sheaths [1]. The Evolution mechanical dilator sheath system (Cook Medical, Bloomington, IN, USA) was introduced as a new hand-powered method for overcoming adhesions and fibrosis that surround chronically implanted leads.

The Evolution sheath is composed of a relatively flexible substance (Teflon) and metal (steel) with threaded metal distal tip which allows the system to pass through adhesions. The external polymer sheath protects the vessel wall by covering the internal metal tip in a telescoping fashion, simultaneously allowing the metal tip to be rotated by the operator for release of adhesions [5]. Few centers have reported cases or case series of their use of Evolution, with only one center reporting it as a first-line choice for extraction [6-8].

In this case series, we report our experience with the Evolution mechanical dilator sheath as first line choice for transvenous lead extraction.

METHODS

Patient population

Our case series included 43 patients who underwent CIED lead extraction between the months of July 2011 and May 2015 in two medical centers: the University of California San Francisco Medical Center (UCSF, San Francisco, CA, USA) and the American University of Beirut Medical Center (AUBMC, Beirut, Lebanon). A total of 88 leads were removed, all using the Evolution system as a first-line choice for extraction. The decision for lead removal was based on the indications stated in the consensus document of the Heart Rhythm Society (HRS) published in 2009 [1]. Blood cultures were drawn from all patients with suspected infection of the CIED pocket or leads and transesophageal echocardiography

was done in case of positive blood cultures to determine the presence of endocarditis and dictate further medical management.

Definitions of success and complications

As per the consensus document of the HRS published in 2009 [1], *complete procedural success* was defined as the “removal of all targeted leads and all lead material from the vascular space, with the absence of any permanently disabling complication or procedure related death”. On the other hand, it was determined that *clinical success* was achieved if all targeted leads and lead material were removed from the venous structure or if the retained portion was too small to cause any negative impact on the outcome of the procedure or the life of the patient. *Failure* was defined as the inability to achieve either of the above or the occurrence of a permanent disability or procedure related death.

Complications were divided into intra-procedural or post-procedural complications. Major complications were outcomes not amenable to intervention and caused a permanent disability, life-threatening consequences or death. Minor complications, on the other hand, were outcomes simple to treat and did not affect the patient’s function or threaten life [1].

Procedure

All patients underwent lead extraction in the electrophysiology laboratory under general anesthesia. Invasive arterial pressure and noninvasive oxygen saturation were monitored in all patients while they were in the electrophysiology laboratory. In patients dependent on bradycardia support, a temporary pacemaker was inserted from the femoral vein.

After opening the pocket, capsulectomy was performed and all at risk tissue was removed. The leads were dissected down to the tie down sleeves. Simple traction or traction on a locking stylet with insulation-bound suture was attempted initially. If this approach was not sufficient, then the Evolution sheath was used for extraction (Figure 1). Binding of the conductor and insulating elements were used to exert control over the lead body and tip.

Three major principles were followed during the procedure: dissection of fibrotic adherences when needed, control of the entire lead body, and countertraction at the tip of the lead. Locking stylets were used to control the conductor coil down to the tip of the lead being extracted. The lead’s outer insulation and conductor usually were bound together by a suture tied at the insulation. All patients were monitored for complications related to the procedure at the time of extraction and during their hospital stay.

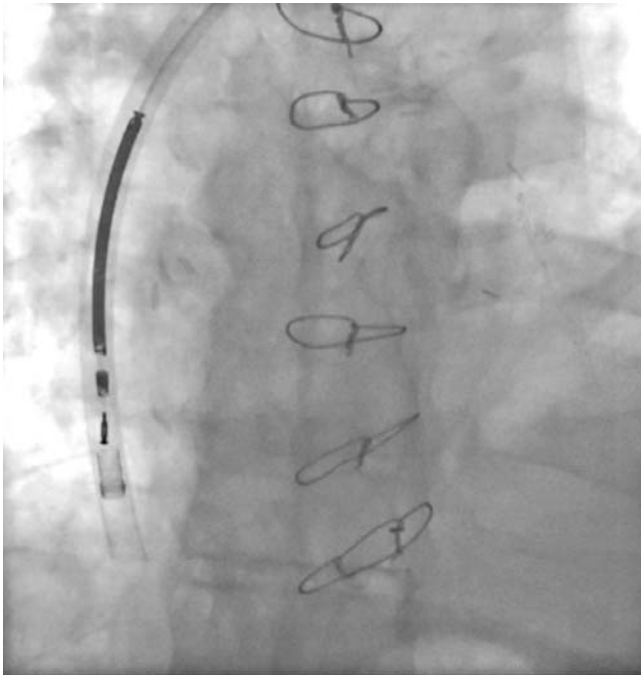


Figure 1

A right ventricular defibrillator lead completely extracted into an Evolution dilator sheath

Statistical analysis

Statistical analyses were performed with STATA 13 software (College Station, TX: Stata Corp LP). All continuous variables are reported as mean \pm standard deviation (SD). All categorical variables are reported as number (percentage).

RESULTS

The Evolution mechanical dilator sheath was first used at AUBMC in July 2011. Between July 2011 and May 2015, the Evolution was used for extraction of 88 leads in 43 patients at UCSF and AUBMC.

Baseline characteristics of the patients are summarized in Table I. Thirty-five patients were male (83.3%). The mean age was 59 ± 11 years.

TABLE I BASELINE CHARACTERISTICS

CHARACTERISTICS	Number	%
Male	35	83.3
Age	$59 (\pm 10.7)$	
Coronary artery disease	17	40.5
Coronary artery bypass graft	7	16.7
Congestive heart failure	15	35.7
Diabetes mellitus II	8	19.1
Hypertension	11	26.2
Lead age (months)	$84 (\pm 10.7)$	

TABLE II OVERVIEW OF EXTRACTED LEADS

EXTRACTED LEADS		
(Total = 88; Total patients = 43)	Number	%
By Type		
Defibrillator lead	32	74.4
Pacemaker lead	11	25.6
By Location		
Atrial	35	39.8
Ventricular	53	60.2
By Approach		
Left-sided	34	79.1
Right-sided	9	20.9
By Indication		
Pocket infection/erosion	17	39.5
Persistent bacteremia	7	16.3
Lead fracture	18	41.9
Subclavian vein stenosis	1	2.3
By Brand		
St. Jude	26	38.2
Biotronik	5	7.4
Medtronic	13	19.1
Ela	2	2.9
Boston Scientific	3	4.4
Unspecified	19	27.9

Similar to what is stated in the literature [3,9] the most frequent indication for lead extraction was an infectious process in 24 patients (55.8%), followed by lead malfunction in 18 patients (41.9%) and subclavian vein stenosis in one patient (2.3%) as shown in Table II. Mean implantation time was 84 months (range 1-270 months). Thirty-two (74.4%) ICD leads and 11 (25.6%) pacemaker leads were extracted. Of the leads extracted, 35 (40%) were atrial and 53 (60%) were ventricular. A right-sided approach was used in nine (20.9%) out of the 43 patients.

The Evolution system was used as first choice in all patients, with 100% clinical success. Complete procedural success was achieved in 38 patients (88.3%), with retention of the distal electrode with the distal end of the RA or RV coil in five patients. These patients on follow-up were cured from their bacteremia and were able to undergo reimplantation of a new CRT-D system.

The presence of multiple leads posed some technical difficulties to the procedure caused by wrapping adjacent leads around each other.

This was occasionally approached by the use of a large diameter Evolution sheath (13 French) that can take two leads at a time allowing extraction of two

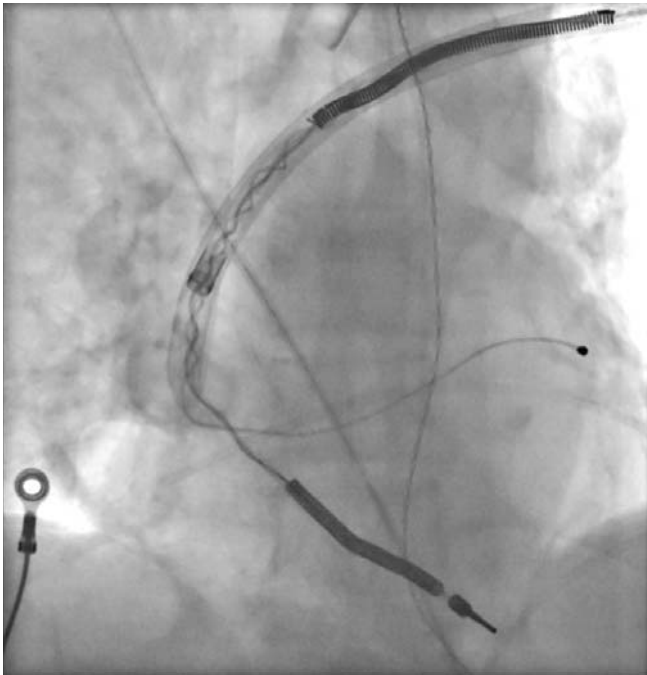


Figure 2

A 13 French Evolution dilator sheath extracting a left ventricular lead and a right ventricular lead simultaneously

leads together (Figure 2). Factors that were associated with partial success were extraction of an ICD lead and the prolonged age of the lead.

No major complications occurred in our cohort. One patient developed hypotension during the procedure. However, an emergent transthoracic echocardiogram revealed no pericardial effusion or cardiac tamponade. The patient's symptoms were transient and responded immediately to intravenous fluids. Another patient developed a pneumothorax and a third patient had a small pericardial effusion, neither of which caused any hemodynamic compromise. There were no deaths.

DISCUSSION

Our data supports the use of the Evolution sheath as a first-line tool given its high rate of clinical and procedural success. As with some of the older extraction methods, the Evolution system proved to be efficient in the release of fibrous material surrounding the targeted leads, allowing for easy removal of problematic leads. In our centers, it was used in the setting of old leads (mean lead age 84 months) and in patients with multiple leads, suggesting its ease of handling and safe maneuverability.

Due to experience and comfort-level among electrophysiologists with other techniques, the Evolution system has been mostly used as an adjuvant, rather than first-line, choice after trying laser/radiofrequency sheaths [7,9].

However, a study similar to ours by Oto *et al.* – including 23 patients (with a total of 41 leads) – resulted in a comparable 91% procedural success rate and 100% clinical success rate [8]. It is also worth noting that approaching such a difficult procedure with one sufficiently successful technique such as the Evolution system will most likely allow for faster extraction, shorter fluoroscopy time and less radiation exposure [7,10]. Complications like those that occurred within our cohort are also infrequent. In a cohort of 212 patients undergoing CIED lead extraction, only three (1.4%) were reported to have pneumothorax or pericardial tamponade [11].

Compared to laser-assisted systems which are costly and limited to institutions that have the required facilities for their use, the Evolution system is a simpler and more cost-effective device that allows the electrophysiologist easier access to extraction tools. Problems were faced with wrapping of leads around the Evolution system but this was overcome with the proper use of the outer sheath that acts as a barrier between the system and the adjacent leads. In addition, the utilization of a large diameter sheath can reduce friction between the tip of the Evolution and the lead, allowing the operator to extract two leads at a time.

The issue of severance of the lead is a major concern and this risk might be less with the laser powered sheath [5,7-8]. This can be a considerable barrier especially when it comes to extraction of leads with inside-out abrasion and externalized conductors [12]. The Evolution system may, therefore, be used as first-line system in transvenous lead extraction in high-volume medical centers with experienced personnel.

Study limitations

There were a few limitations to our study. First, the small number of patients limits the significance of the results, despite a high success rate and a negligible rate of complications. Second, the results were a single operator's experience and, thus, cannot be generalized since the outcomes may differ from center to center as well as from operator to operator, due to differences in level of training. Furthermore, there is the lack of randomization. As previously mentioned, this study is a retrospective cohort in which our experience with the Evolution system was reviewed. However, no comparison of safety and efficacy was made between the Evolution system and other devices available for lead extraction in a randomized controlled trial.

CONCLUSION

To our knowledge, our data is among the first and few reported case series where the Evolution system was

used as the first-line choice for CIED lead extraction [8], as opposed to a rescue or second-line approach. Our data, though with a limited number of patients, suggest that it is a safe, efficient and likely cost-effective strategy to manage problematic CIED leads.

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CARDIAC ARRHYTHMIAS THE ASSOCIATION OF DIABETES, ATRIAL FIBRILLATION AND VENTRICULAR ARRHYTHMIAS

<http://www.lebanesemedicaljournal.org/articles/67-1/review1.pdf>

Muhie Dean SABAYON¹, Charbel ABI KHALIL^{2,3}, Mohammad SABRA⁴, Fouad A. ZOUZEIN^{5*}, Marwan M. REFAAT^{4*}

Sabayon MD, Abi Khalil C, Sabra M, Zouein FA, Refaat MM. The association of diabetes, atrial fibrillation and ventricular arrhythmias. *J Med Liban* 2019; 67 (1): 28-33.

Sabayon MD, Abi Khalil C, Sabra M, Zouein FA, Refaat MM. Relation existant entre diabète, fibrillation auriculaire et arythmies ventriculaires. *J Med Liban* 2019; 67 (1): 28-33.

ABSTRACT • Recent evidence suggests that diabetic patients are at increased risk to develop arrhythmias. This brief review presents this evidence and the relationship between diabetes mellitus (DM) and arrhythmias, specifically atrial fibrillation (AF) and ventricular arrhythmias (VAs).

Animal studies have demonstrated that hyperglycemia induces oxidative stress that results in myocardial injury and cell ischemia which predispose to AF. Furthermore, prolonged hyperglycemia results in the formation of advanced glycosylation end products which invade the myocardium and lead to diabetic cardiomyopathy forming a substrate for anatomic and electrical atrial remodeling predisposing to AF as well.

Patients with DM and without known cardiovascular disease have significantly higher incidences of T-wave alternans (TWA) than non-DM patients. These TWA occurrences are positively correlated to HbA1c level. DM also produces a diabetic myocardium vulnerable to VAs and plays a crucial role in triggering these arrhythmias.

In conclusion, further randomized controlled trials are needed to verify the mechanisms that result in arrhythmias in patients with DM and which lead to major cardiovascular complications and mortality. The focus of interventions should be based on primary prevention of diabetes, coronary artery disease, and atherosclerosis until novel mechanism-based approaches that reduce arrhythmias in patients with DM are established

Keywords : diabetes mellitus; atrial fibrillation; ventricular arrhythmias

RÉSUMÉ • Des études récentes suggèrent que les patients diabétiques présentent un risque accru de développer des arythmies. Cette brève revue présente ces preuves et la relation entre le diabète et les arythmies, en particulier la fibrillation auriculaire (FA) et les arythmies ventriculaires (AVs).

Des études chez l'animal ont montré que l'hyperglycémie induisait un stress oxydatif qui entraînait des lésions du myocarde et une ischémie cellulaire prédisposant à la FA. En outre, une hyperglycémie prolongée entraîne la formation de produits finaux de glycosylation avancés qui envahissent le myocarde et conduit à une cardiomyopathie diabétique formant un substrat pour le remodelage auriculaire anatomique et électrique prédisposant également à la FA.

Les patients atteints de diabète et sans maladie cardiovasculaire connue ont une incidence significativement plus élevée d'alternance à l'onde T que les patients non diabétiques. Le diabète produit également un myocarde diabétique vulnérable aux AVs et joue un rôle crucial dans le déclenchement de ces arythmies.

En conclusion, d'autres études contrôlées randomisées sont nécessaires pour vérifier les mécanismes qui entraînent des arythmies chez les patients atteints de diabète et qui conduisent à des complications cardiovasculaires majeures et à la mortalité. Les interventions devraient être axées sur la prévention primaire du diabète, de la maladie coronarienne et de l'athérosclérose jusqu'à ce que de nouvelles approches fondées sur des mécanismes permettant de réduire les arythmies chez les patients atteints de diabète soient établies.

Mots-clés : diabète; fibrillation auriculaire; arythmies ventriculaires

INTRODUCTION

Diabetes is a cardiovascular risk factor that results in significant morbidity and mortality [1]. Even though coronary artery disease is the most well-established diabetic cardiovascular complication, recent evidence suggests that diabetic patients are at increased risk to develop arrhythmias [2]. Some of the mechanisms that generate

an arrhythmogenic substrate in diabetic patients include: autonomic imbalance, silent ischemia, inflammation, genetic predisposition, and QTc prolongation (Table I). Other mechanisms exist as well. In this brief review, the relationship between diabetes mellitus and arrhythmias, specifically atrial fibrillation and ventricular arrhythmias will be presented.

¹Department of Cardiology, Emory University School of Medicine, Atlanta, Georgia.

²Adult Cardiology, Heart Hospital, Hamad Medical Corporation, Doha, Qatar.

³Department of Medicine and Genetic Medicine, Weill Cornell Medicine, Doha, Qatar.

⁴Department of Cardiology, American University of Beirut Medical Center, Beirut, Lebanon.

⁵Department of Pharmacology and Toxicology, American University of Beirut & Medical Center, Beirut, Lebanon.

*Equal contribution.

Corresponding authors: *Marwan M. Refaat, MD.* mr48@aub.edu.lb & *Fouad Antoine Zouein. PhD* fz15@aub.edu.lb

TABLE I ARRYTHMIAS AND ASSOCIATED PATHOPHYSIOLOGY

Arrhythmia	Pathophysiology	Studies
Atrial fibrillation	Lipotoxicity	Boudina <i>et al.</i> ¹⁰
	Formation of AGEs	Morrow <i>et al.</i> ¹⁶ , Liu <i>et al.</i> ²⁰ , Kato <i>et al.</i> ²¹ , Igarashi <i>et al.</i> ²²
	Pulmonary vein ganglia remodeling	Bassil <i>et al.</i> ¹⁹
	Genetic mutations	Kirchhof <i>et al.</i> ²⁵ , Arnar <i>et al.</i> ²⁶ , Ellinor <i>et al.</i> ²⁷ , Fatini <i>et al.</i> ²⁹
Ventricular arrhythmia	Prolonged QTc	Cardoso <i>et al.</i> ⁵¹
	T-wave alternans	Molon <i>et al.</i> ⁵²
	Autonomic neuropathy	Vinik <i>et al.</i> ⁵³

Atrial fibrillation and diabetes mellitus

Atrial fibrillation (AF) is the most common arrhythmia worldwide. With the ageing population, the prevalence of AF is going to increase by 2.5-fold in the next 50 years [3]. AF is associated with multiple complications including heart failure (HF) and thromboembolism, and it significantly increases mortality [4]. A concomitant disease in patients with AF [5], diabetes mellitus (DM) has become a major pandemic over the past few decades in the western world as well as developing countries due to over-nutrition, sedentary habits and genetic predisposition. AF and DM share common antecedents such as obesity, atherosclerosis and hypertension [6], and the causal relationship between them shall be discussed.

The Framingham Heart Study showed that AF is one of the main cardiovascular complications associated with DM. DM conferred an odds ratio of 1.4 for men and 1.6 for women, after multivariate adjustment, for developing AF [7] (Table II). In the same study, AF incidence in patients with diabetes was 14.9%; furthermore, atrial flutter occurs in 4% of diabetic patients compared with 2.5% in the control group [8]. Moreover, metabolic syndrome, which is interrelated to obesity as well as DM, is a well-established risk factor for AF [9].

Another possible pathophysiological mechanism linking obesity with DM and AF is the “lipotoxicity theory” whereby the accumulation of adipose tissue results in diabetic cardiomyopathy and myocardial lipotoxicity which in turn result in myocardial inflammation and oxidative stress that is followed by autonomic dysfunction, myocardial fibrosis and fatty infiltration which in

turn result in reentry (stabilized), followed by ectopic activity and hence, AF [10].

The relationship between AF and DM is that of great significance. Because of the silent progression of DM, many cases of DM remain undiagnosed until they reach an advanced stage. During this time, many DM-related complications would be progressing without treatment for quite some time. Thus, when AF occurs in this population it would carry a worse prognosis and a higher mortality rate [11]. Hence, efforts have been made to understand the altered molecular pathways in DM patients that may affect the initiation and/or progression of AF.

The mechanism of AF is still elusive. The current unified electrophysiological hypothesis of how AF initiates and perpetuates is that focal areas localized to the inside of pulmonary veins (PVs) are what trigger the initiation of reentry circuits which over time result in atrial remodeling which results in additional focal triggers that perpetuate microwave reentry [12]. Ionic currents across the cardiac myocyte which are products of the five phases of the cardiac action potential can cause arrhythmogenesis when alterations in the cardiac action potential duration (APD) occurs. Vernakalant and amiodarone are atrial peak INa blockers that have an established therapeutic effect on the suppression of AF because of their rate-dependent reduction of excitability, prolongation of ADP and hence, effective refractory period (ERP). Reduction of intracellular calcium loading via late INa inhibition may suppress triggers that initiate AF especially in the setting of prolonged ADP and bradycardia [13]. Ranolazine, a late INa current blocker, has been shown to reduce reactive oxygen species (ROS) hydrogen peroxide-induced arrhythmogenic activity in rabbits and pigs by prolongation of the ADP due to reactive species [14]. Furthermore, in the post hoc analysis of the MERLIN-TIMI 36 trial, ranolazine which was given in patients with acute coronary syndrome led to fewer episodes of new onset AF with a lower overall AF burden [15]. Ranolazine also significantly reduced the levels of HbA1c in diabetics in the same group and reduced the incidence of increased HbA1c in patients without evidence of previous hyper-

TABLE II

DIABETES MELLITUS: RISK FACTOR FOR ATRIAL FIBRILLATION	
Studies	Diabetes mellitus & Atrial fibrillation
Framingham Study ⁷	DM + AF = 1.4 in males = 1.6 in females
ALFA study ⁵⁶	DM in chronic AF patients 13%
Manitoba study ⁵⁷	Age specific incidence of AF in 4000 males DM + AF = Relative risk of 1.8
DM: diabetes mellitus AF: atrial fibrillation	

glycemia [16]. In addition, ranolazine is effective in the facilitation of restoration of sinus rhythm when added to amiodarone (especially in patients with dilated atria) [17]. The HARMONY trial has also validated ranolazine's synergistic effect with dronedarone [18]. For these reasons, ranolazine proves to be an effective therapeutic option for AF in diabetic patients.

In their study on mice models, Bassil *et al.* showed that Type 1 DM causes pulmonary vein ganglia remodeling specifically hypotrophy of the cell bodies of sympathetic and parasympathetic cell bodies. The concomitant autonomic dysfunction through the decrease in sympathetic and parasympathetic function has been directly linked to the initiation of AF [19].

In humans, the mechanism by which hyperglycemia leads to the development of AF is still unknown. However, animal studies have demonstrated that hyperglycemia induces oxidative stress that results in myocardial injury and cell ischemia which predispose to AF [20]. Rabbit models demonstrated that hyperglycemia induces atrial interstitial fibrosis and atrial electrical remodeling. [16]. This electrical remodeling has been shown to be associated with advanced glycation end (AGE) products/receptor for AGE system [21] and overexpression of a gap junction protein Cx43 which predispose to AF [22]. In humans, deposition of collagen and AGE products in the myocardial extracellular matrix as well as the accumulation of intramyocellular triglycerides occur with increased myocardial stiffness which occurs in diastolic dysfunction [23,24]. Furthermore, insulin resistance is independently associated with increased atrial size, a known risk factor for the development of AF [24].

AF can also be a heritable disease [25]. Single gene mutations common in families with AF [26] as well as genetic variants of AF in the general population [27] have been identified. For example, the *connexin 40* (Cx40) gene carrier has a significantly higher risk for developing AF [28].

Similarly, patients with polymorphisms involving the *minK* and *eNOS* genes are more predisposed to developing non-valvular AF [29]. These mutations affect genes which encode transcription factors regulating the electrical stability of the atrium as well as atrial remodeling (by influencing the atrial conduction velocity). Hence, they shorten cellular refractory periods and increase the automaticity of PVs foci [30]. An example of this is the transcription factor nuclear factor-kappa B (NF-KB). NF-KB promotes reentry by enhancing conduction heterogeneity, by affecting redox signaling pathway or angiotensin cascade [31]. In DM, hyperglycemia causes an overproduction of ROS which leads to NF-KB upregulation which promotes the transcription of pro-inflammatory genes hence promoting an inflammatory state [32].

Because of the role of NF-KB in mediating an inflammatory state in DM and the genesis of AF, therapy targeting NF-KB to suppress AF in diabetic patients is very appealing. However, currently no clinical studies are available to confirm this hypothesis.

Similarly, the transcription factor peroxisome proliferator-activated receptor gamma (PPAR-gamma) has been proven to have anti-inflammatory and anti-oxidant effects [33]. Furthermore, in elderly patients with AF, there is a strong correlation between lower levels of PPAR-gamma receptor protein and higher serum levels of inflammatory markers such as hs-CRP, IL-6 and TNF-alfa [34]. Thiazolidinediones (TZDs), in addition to their anti-diabetic activity, are PPAR-gamma activators which have been found to independently protect diabetic patients from the development of AF by Chao and colleagues after adjustment for other variables [35]. Moreover, TZDs may delay the progression of persistent AF to permanent AF in diabetic patients by affecting atrial remodeling via their effect of reducing circulating levels of pro-collagen type I carboxy terminal peptide (PICP) and advanced glycosylation end products (AGEs) [36]. Thus, further randomized controlled trials aimed to confirm these therapeutic effects of TZDs in patients with DM and AF are needed.

Prolonged hyperglycemia results in the formation of AGEs which invade the myocardium and lead to interstitial fibrosis, hypertrophy and eventually diabetic cardiomyopathy which results in a substrate for anatomic and electrical atrial remodeling [10]. Thus, the interstitial fibrosis that forms this substrate is what promotes anisotropic impulse propagation which accounts for the initiation and perpetuation of microwave reentry which begets AF. A positive linear correlation between HbA1c and risk of AF in patients with and without DM is well established [37]. However, as per the ACCORD cohort, intensive glycemic control does not affect the rate of new-onset AF [38]. In fact, patients with DM and AF had an increased risk of morbidity and mortality compared to those without AF. On the other hand, Pathak *et al.* highlighted the role of lifestyle modifications in the treatment as well as prevention of AF. They proved that long-term sustained weight loss (including avoidance of weight fluctuation) is associated with significant reduction of AF burden and maintenance of sinus rhythm in patients with BMI > 27 kg/m², and that a weight reduction of more than ten percent resulted in more than 6-fold of arrhythmia free survival compared to other less strict weight loss measurements (95% CI: 3.4-10.3, *p* < 0.001) [39]. Hence, targeting weight loss should be the first line therapy in DM obese patients with AF referred for AF therapy. This importance of aggressive risk factor modification and its effect on AF maintenance has also been

described in the ARREST-AF trial which showed in DM patients with AF who underwent AF catheter ablation, the odds of arrhythmia free survival increased 5-fold after aggressive risk factor modification [40].

The risk for ischemic stroke and hence worse outcome has been proven to be increased in patients with DM [41]. A main factor that triggers ischemic stroke in patients with DM is the occurrence of AF [42]. Patients with AF and DM have exaggerated endothelial dysfunction than patients without DM and this explains why this population might be at higher risk of developing strokes [43]. Vitamin K antagonists, for decades, have been the cornerstone for treatment of patients who are at high risk for thromboembolic disease. However, it has been shown that DM is one of the clinical factors that affects anticoagulation control during warfarin therapy. This has been demonstrated by the SAME-TT₂R₂ score [44]. Hence, warfarin therapy might not be the best treatment option in diabetic patients with AF.

Furthermore, trials comparing novel anticoagulants to warfarin (namely: RE-LY [45], ROCKET-AF [46], ARISTOTLE [47], and ENGAGE-AF [48]) well represented patients with DM and outcomes were comparable to those without DM. These trials proved that the relative efficacy and safety of the new anticoagulants was similar in patients with DM compared to patients without DM. Hence, it is reasonable to consider one of the new anticoagulants as first line therapy to prevent thromboembolic events in patients with DM and AF.

Ventricular arrhythmias and diabetes mellitus

The leading cause of death in patients with DM is cardiovascular disease. DM enhances atherosclerosis and coronary artery disease, and this high incidence and extent of coronary atherosclerosis inevitably results in ventricular arrhythmias (VAs) and sudden cardiac death (SCD) [49] (Table III). The presence of other noncoronary atherosclerotic factors also play a role in strengthening the interrelation between DM, VAs and SCD. These factors include: autonomic neuropathy, microvas-

cular disease, and ventricular electrical and structural changes [50].

Several recent studies have proven that patients with DM have prolonged QTc intervals compared to patients without DM which places these patients at a high risk for VAs [51]. Microvolt T wave alternans (TWA), another strong predictor of VAs, has also been studied in patients with DM [52]. Patients with DM and without known CVD, had significantly higher incidences of TWAs than non-DM patients; furthermore, these TWA occurrences positively correlated to the HbA1c level. For every 1% rise in HbA1c, there was a 13-fold increase in the risk of having atypical TWAs which resulted in a higher risk of spontaneous VAs. This was independent of the QTc interval duration. These trials conclude that the diabetic myocardium is electrically unstable creating potential substrates for reentry and hence VAs. This substrate is different from that of ischemic cardiomyopathy in which the substrate is scar tissue resultant from ischemia. Furthermore, autonomic neuropathy also renders this diabetic myocardium electrically unstable by perpetuating unbalanced sympathetic stimulation which predisposes to VAs [53]. In addition, cardiac sensory neuropathy predisposes to VAs and SCD via silent ischemia [54].

Not only does DM produce a diabetic myocardium vulnerable to VAs, it seems to play a crucial role in triggering these arrhythmias as well. Chen-Scarabelli and colleagues showed that suboptimal glycemic control and persistent hyperglycemia are associated with a higher risk of developing VAs [55].

CONCLUSION:

The pathophysiological and electrophysiological mechanisms (Table I) that result in arrhythmias in patients with DM lead to major cardiovascular complications as well as mortality. Further randomized controlled trials are needed to verify these mechanisms further. We still lack a detailed comprehension of the molecular cues linking hyperglycemia, insulin resistance with arrhythmogenic substrates. Until then, the focus of interventions should be based on primary prevention of diabetes, coronary artery disease, and atherosclerosis until novel mechanism-based approaches to reduce arrhythmias in patients with DM are established.

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Studies	Diabetes mellitus & Sudden cardiac death
Framingham Study ⁷	DM increases risk of SCD in all age groups SCD is higher in DM women > Men
Nurse Health Study ⁵⁸	DM 3x risk of SCD (HTN 2.5, obesity 1.6)
Honolulu Heart Program ⁵⁹	DM & MI increase RR of SCD than non DM
Paris Prospective Study ⁶⁰	DM is a strong risk factor for SCD in the French population

DM: diabetes mellitus SCD: sudden cardiac death HTN: hypertension
MI: myocardial infarction RR: relative risk

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CARDIAC ARRHYTHMIAS

ELECTROCARDIOGRAPHIC PREDICTORS OF OUTCOME AFTER RADIOFREQUENCY CATHETER ABLATION OF FREQUENT NON-ISCHEMIC PREMATURE VENTRICULAR COMPLEXES

<http://www.lebanesemedicaljournal.org/articles/67-1/original6.pdf>

Maysam M. AL-HOUSARI¹, Maurice KHOURY¹, Marwan M. REFAAT¹, Bernard HARBIEH¹, Bernard ABI-SALEH^{1*}

Al-Housari MM, Khoury M, Refaat MM, Harbieh B, Abi-Saleh B. Electrocardiographic predictors of outcome after radiofrequency catheter ablation of frequent non-ischemic premature ventricular complexes. *J Med Liban* 2019; 67 (1): 34-41.

ABSTRACT • Background: Radiofrequency catheter ablation (RCFA) improves or prevents deterioration of left ventricular function in patients with frequent premature ventricular contractions (PVCs). We aim to identify predictors of outcome of this procedure. **Methods:** This is a retrospective, single center study of patients with frequent non-ischemic PVCs undergoing RFA at our center. Medical charts of 63 patients were reviewed for multiple patient- and PVC-related variables, and analyzed to correlate with acute and chronic procedural outcome. **Results:** The predominant PVC (pPVC) was acutely terminated in 53 patients (84.1%), > 80% reduced at one to three months in 54 patients (85.7%), and recurred in two patients. The presence or absence of the pPVC 12 hours post-procedure was the single most significant predictor of long-term outcome (sensitivity 94.4%, positive predictive value 96.2%). PVC QRS transition from negative to positive at V3 was significantly associated with acute procedural failure (p -value 0.02); the transition on V4 was significantly associated with procedural outcome showing a 100% success rate both acutely and on follow-up (p -value < 0.05). Patients with failed outcome at one to three months were more likely to have congestive heart failure (p -value 0.025). **Conclusion:** Acute outcome within 12 hours of non-ischemic PVC ablation is the most significant predictor of outcome at one to three months post procedure. PVC transition at V4 is highly associated with procedural success while transition at V3 might be predictive of failed ablation.

Keywords: electrocardiogram; outcome; predictors; premature ventricular complexes; radiofrequency catheter ablation

INTRODUCTION

Frequent premature ventricular complexes (PVCs), defined as more than 60 PVCs per hour (> 1/min), is the most common arrhythmia in patients with structurally normal hearts, with an estimated prevalence of 1 to 4% of the general population [1,2]. Although previously considered a benign condition [3], frequent PVCs which are associated with a twofold increased risk of stroke and mortality [4,5], have also recently been shown to have a

detrimental effect on left ventricular (LV) function whether in the form of overt cardiomyopathy or in the form of early subclinical changes as detected by 2D speckle strain echo imaging [6-8].

Radiofrequency catheter ablation (RFCA) is indicated in symptomatic cases with refractory PVCs despite medical therapy with antiarrhythmic and/or β -blockers or to prevent LV dysfunction [9,10]. With high reported success rates and low complication rates (< 1%) for outflow tachycardias [11-15], RFCA carries a Class I indication for right ventricular outflow tract (RVOT), ventricular arrhythmias (VAs) and Class IIa for left ventricular outflow tract LVOT VAs, if performed in experienced centers [16]. Elimination of frequent PVCs by RFCA has been shown to improve LV function and to prevent deterioration of the LV systolic function [17-20].

Several factors have been associated with failure of PVC ablation e.g. inability to reach the site of origin (SOO) particularly in epicardial or intramural arrhythmias [21,22], or inability to identify the SOO because of imprecise mapping (as in pace mapping) [23]. There is also around 15% risk of recurrence at three months after acutely effective RFCA as shown in a recent study [24].

Limited data is available in the literature regarding predictors of outcome of RFCA of PVCs [24-26]. This study aims at correlating between multiple PVC and patient-related variables, and outcome at one-to-three months post ablation procedure.

METHODS

This is a retrospective, single center study of a series of 63 patients (age: 48 years \pm 14, males: 56%, EF 53.4% \pm 9.5%) with frequent non ischemic PVCs who underwent RFCA of their predominant PVC at our center between January 2012 and December 2016.

Medical charts were reviewed for initial PVC burden, acute post procedural outcomes and long-term outcome assessed at 1-to-3 months after the ablation procedure. To study the predictors of procedural outcome, multiple patient- and PVC-related variables were analyzed including: age, sex, comorbidities (diabetes mellitus, hypertension, coronary artery disease, LV dysfunction, dyslipidemia), smoking, left ventricular ejection fraction (LVEF), anti-arrhythmic therapy

¹From Cardiac Electrophysiology Section/Cardiology Division American University of Beirut Medical Center, Lebanon.

*Corresponding author: Bernard Abi-Saleh, MD.
e-mail: ba47@aub.edu.lb

(β -blockers, calcium channel blockers, class III antiarrhythmic), PVC burden, site of origin, and QRS transition from negative to positive on 12 lead ECG.

The PVCs were classified as originating from right ventricular outflow tract (RVOT, including pulmonary artery), left ventricular outflow tract (LVOT), aortic cusps, aorto-mitral continuity, mitral annulus, and LV summit. All cases included had endocardial ablation.

We excluded those with papillary muscles, epicardial, fascicular or any scar related origins.

Patients included had failed medical therapy with a β -blocker or calcium channel blocker with or without antiarrhythmic medications. Left ventricular ejection fraction was determined through echocardiography results, and patients with or without PVC-induced cardiomyopathy were included. Patients with pleomorphic PVCs (different morphology from the predominant PVC by at least three leads of the 12-lead ECG) were also included whether ablation targeted only the predominant PVC or multiple PVC morphologies.

All patients had a 24-hour Holter monitor recording prior to their ablation from which PVC burden was determined. Twelve-lead telemetry monitor was used to detect any PVC recurrence during the 12 to 24 hours post ablation observation period. Telemetry monitors are routinely reviewed the day following the ablation for any recorded arrhythmias. Holter recording and 12-lead ECG were repeated at follow-up 1-to-3 months post ablation procedure.

Acute procedural outcomes were defined as: acutely successful if the predominant PVC was completely eliminated (after at least one hour of the last ablation delivered) and did not recur for the 12 to 24 hours period monitored by telemetry, partially effective procedure if there was significant decrease in PVC burden of more than 50% in the first 12-24 hours post ablation period and failed if the ablation was not attempted due to a high risk proximity to vital structures, or if it could not be terminated at the end of the procedure, and if it recurred within the first 24-hour observation period after an effective initial procedure.

One-to-three months outcomes were defined as: successful if there was at least 80% decrease of the initial PVC burden, partially effective if the PVC burden was reduced by 50-80% of the initial one and failed if the PVCs persisted with less than 50% reduction of the initial PVC burden.

Antiarrhythmic medications were discontinued five half-lives before the ablation procedure.

After successful ablation all patients had their antiarrhythmic medication discontinued. Beta-blockers and calcium channel blockers were also discontinued unless there was another indication for their continuation.

Electrophysiology procedure

Informed consent was obtained in all cases. Conscious sedation was used, and none of the cases received general anesthesia. Femoral vein access was obtained and when arterial access was also needed for left-sided ablations heparin was started targeting an activated clotting time of 250-300 seconds. Phased-array ICE (Saint Jude Medical, Saint Paul, MN) was routinely utilized for all LVOT/aortic cusps mapping.

An octapolar deflectable CS catheter was used to record coronary sinus intracardiac tracings and as a reference for the electroanatomic mapping. The ablation catheter was used at first at the HIS position to record baseline measurements, and at the RV in case programmed stimulation was needed to induce ventricular tachycardia.

Thermocool 3.5 mm open irrigated tip, or Flexibility 4mm open irrigated tip ablation catheters were used to map the PVCs. Activation mapping of the PVCs was performed using NAVX Velocity 3D electroanatomic mapping system (NavX, St Jude Medical, St Paul, MN).

Irrigated RF was delivered at the site of origin using power of 30-40 W (15-20 W in case of aortic cusps ablations). In case of pleomorphic PVC, non-predominant PVCs were not targeted unless they were frequent.

Isoproterenol and sometimes caffeine were used to increase PVCs burden if they were not frequent enough for activation mapping during the procedure, and at the end of successful procedures to challenge for PVC recurrence, during the 60 minutes observation period in the EP laboratory.

Statistical analysis

Continuous variables were expressed as mean \pm 1 standard deviation and were compared with Mann-Whitney U test for $N < 30$.

Categorical variables were compared with the χ^2 test. If the sample size was smaller than 5 in a given cell, Fisher's exact test was used. A p -value < 0.05 was considered statistically significant.

Paired sample t -tests were used to compare PVC burden before and after ablation.

RESULTS

Patient and PVC characteristics

Among the 63 patients included in this study, 35 (55.6%) were males, the mean age was 47.7 ± 14 years, and the mean left ventricular ejection fraction was $53.4 \pm 9.5\%$ (Table I).

Eighteen patients (29%) had an impaired left ventricular ejection fraction, 16 of whom had pure PVC-induced cardiomyopathy; one had worsening LV function on top

of baseline ischemic cardiomyopathy, and one on top of dilated cardiomyopathy secondary to mitral regurgitation.

One patient had undergone a prior failed attempted ablation procedure. All patients were on either a β -blocker (56 patients, 89%) or a calcium channel blocker (12 patients, 19%) with or without an antiarrhythmic drug as detailed in Table I.

The mean pre-ablation PVC burden was $25.5\% \pm 10\%$. Eight patients (12.7%) had pleomorphic PVCs. The most common site of PVC origin was the right ventricular outflow tract in 36 patients (57.1%), followed by the aortic cusps in 12 patients (19%), then the left ventricular outflow tract, the aorto-mitral continuity, and the mitral annulus each with 4 patients (6.3%) as shown in Figure 1 and Table I.

TABLE I
BASELINE CHARACTERISTICS OF PATIENTS AND PREMATURE VENTRICULAR COMPLEXES*

Patients, n	63
Male gender, n	35 (55.6%)
Age (years)	47.7 ± 14
Left ventricular ejection fraction (%)	53.4 ± 9.5
Comorbidities, n	
Systolic dysfunction	18 (28.6%)
Coronary artery disease	5 (8%)
Diabetes mellitus II	6 (9.5%)
Hypertension	21 (33.3%)
Dyslipidemia	15 (24%)
Smoking	19 (30%)
Medications, n	
Beta-blockers	56 (89%)
Calcium channel blockers	12 (19%)
Class I antiarrhythmic drug	18 (28.6%)
Class III antiarrhythmic drug	10 (16%)
ACEI/ARB	911 (17.5%)
PVC site of origin, n	
RVOT	36 (57.1%)
Cusps	12 (19%)
LVOT	4 (6.3%)
Aorto-mitral continuity	4 (6.3%)
Mitral annulus	4 (6.3%)
LV summit	3 (4.8%)
PVC transition zone, n	
V1	10 (16%)
V2	10 (16%)
V3	24 (38%)
V4	19 (30%)

*Continuous variables are shown as mean \pm 1 standard deviation. Categorical variables are shown as number (%)

ACEI: angiotensin converting enzyme inhibitor **LV:** left ventricle
ARB: angiotensin II receptor blockers **LVOT:** left ventricular outflow tract
PVC: premature ventricular complexes **RVOT:** right ventricular outflow tract

The most common site of PVC QRS transition from negative to positive on 12-lead ECG was on lead V3 in 24 patients (38%) followed by lead V4 in 19 patients (30%) as shown in Figure 1 and Table I.

Procedural outcome

The predominant PVC was acutely terminated in 53/63 patients (84.1%), and its burden was reduced with more than 80% at 1-to-3 months in 54/63 patients (85.7%). None of the acutely terminated 53/63 had PVC recurrence at 12 to 24 hours. Two patients with initial PVC termination had recurrence at 1-to-3 months.

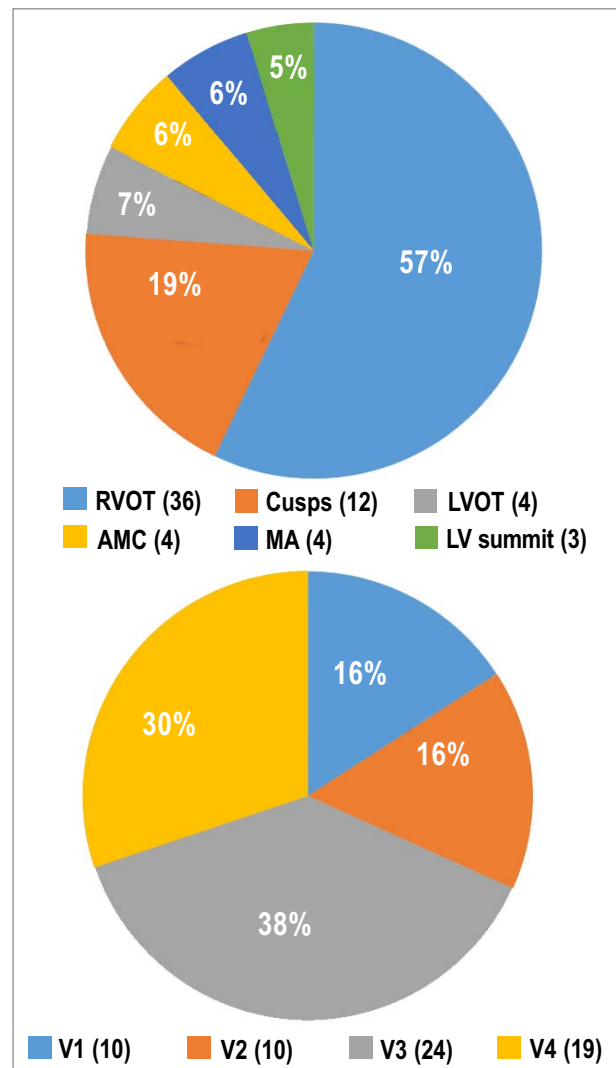


Figure 1

The frequencies of the sites of origin (A) and the transition zones from negative to positive on 12-lead ECG of the predominant premature ventricular contraction (B).

V1, V2, V3 and V4 are the precordial leads.
AMC: aorto-mitral annulus **LV:** left ventricle
LVOT: left ventricular outflow tract **MA:** mitral annulus
RVOT: right ventricular outflow tract.

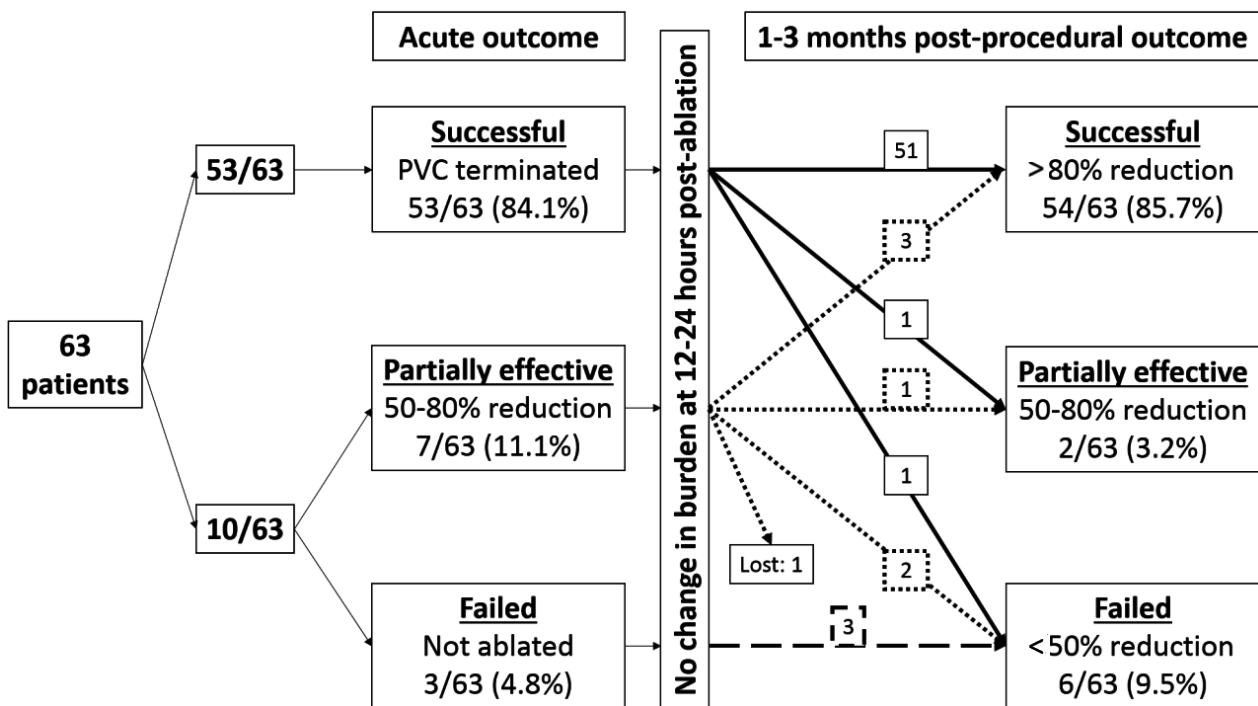


Figure 2. Flow chart of patients acutely post procedure and at 1-to-3 months follow-up.

→ Progression of patients with acutely successful procedure → Progression of patients with acutely partially successful procedure;
 ----→ progression of patients with acutely failed procedure.

In 10/63 patients (15.9%), the predominant PVC was not acutely eliminated: 7 (11.1%) had partially successful procedure with 50-80% reduction in PVC burden at 12-24 hours, and 3 (4.8%) were not ablated, two of which were not attempted because of high risk proximity to the left main origin and to HIS bundle and the third could not be ablated because it was deep intramuscular and the procedure was complicated by tamponade.

At follow-up, three patients (3/10) had > 80% reduction of PVC burden at 1-to-3 months, the origin of which were deep between posteromedial RVOT and right coronary cusp (RCC), posteromedial RVOT just below pulmonary valve, and low posterior RVOT between the HIS bundle and the slow pathway. One patient (1/10) with an origin close to the left main coronary artery had 50-80% reduction at follow-up. Two patients (2/10) had ≤ 50% reduction at follow-up: one had an origin just above pulmonary valve, and the second had an origin at the LV summit with suboptimal ablation lesions as a result of high temperature. One patient (1/10) was lost to follow-up at one month (Figure 2).

The mean PVC burden was reduced from 25.5% ± 10% to 2.9% ± 5.3% at 1-to-3 months post ablation (*p*-value < 0.0001). At follow-up, 54/63 patients (85.7%) had > 80% reduction of the initial PVC burden and 56/63 patients (88.9%) had at least 50% reduction of their initial PVC burden.

Pleomorphic PVCs

More than one PVC morphology was found in 8/63 patients (12.7%). The predominant PVC was successfully terminated in 7 patients and 50-80% acutely reduced in one patient.

In one patient, a non-predominant PVC just lateral to the predominant one was ablated. In another the non-predominant PVC was mapped but not ablated due to proximity to left main coronary artery origin. In five patients the non-predominant PVCs were not attempted due to their low burden. In one case the non-predominant PVCs were targeted but the procedure was aborted due to right femoral artery dissection.

Five patients with pleomorphic PVCs had < 1% PVC burden at 1-to-3 months. One patient had recurrence of the predominant PVC with a total burden of 4% at follow-up. The last two had 3%, and 7% residual PVCs at follow-up for an initial burden of 17% and 40% respectively, but they were found to be of the non-predominant PVC morphology. The PVC burden at follow-up was evaluated according to total PVCs and not according to each PVC morphology due to technical limitations (from referred cases).

Predictors of outcome

The presence or absence of the predominant PVC in the 12-24 hours post procedure period was the single most

significant predictor of outcome at 1-to-3 months of follow-up (p -value < 0.0001) with a sensitivity of 94.4%, a positive predictive value of 96.2%, a specificity of 75%, and a negative predictive value of 66.7%.

Compared to the patients with acutely successful procedural outcome, the patients with acutely failed procedures ($< 80\%$ reduction of PVC burden acutely) had a higher prevalence of PVC transition from negative to positive at V3 (70% vs. 32.1%; p -value 0.024). On the other hand, all 19 patients who had PVC transition from negative to positive at V4 had successful termination acutely (35.8% vs. 0; p -value 0.023), and no recurrence

at 1-to-3 months (35.2% vs. 0; p -value 0.044) as shown in Table II.

Similarly, patients with failed outcome at 1-to-3 months of follow-up had a higher prevalence of PVC transition at V3 (62.5% vs. 33.3%; p -value 0.1) than patients with a successful outcome ($> 80\%$ reduction of PVC burden), and were more likely to have congestive heart failure (62.5% vs. 24.1%; p -value 0.025).

Site of origin and transition zone

We could not find a statistically significant correlation between PVC SOO and outcome, neither acutely nor at

TABLE II
CHARACTERISTICS OF PATIENTS AND PREMATURE VENTRICULAR COMPLEXES
IN RELATION TO THE OUTCOME OF THE PROCEDURE, ACUTELY AND AT 1-TO-3 MONTHS*

PVC transition zone	Acute absence of PVC N = 53 (100%)	Acute presence of PVC N = 10 (100%)	p value	$> 80\%$ PVC reduction on follow-up N = 54 (100%)	$< 80\%$ PVC reduction on follow-up N = 8 (100%)	p value
Male gender	29 (54.7%)	6 (60%)	0.758	29 (53.7%)	5 (62.5%)	0.719
Age (years)	48.3 \pm 14	44.7 \pm 15	0.371	48 \pm 14	50 \pm 12.7	0.825
LVEF (%)	53.6 \pm 9.5	52.4 \pm 9.8	0.698	54.2 \pm 9.2	48 \pm 11	0.15
Medications						
ACEI/ARB	9 (17%)	2(20%)	0.818	8 (14.8%)	3 (37.5%)	0.117
BB	49 (92.4%)	7 (70%)	0.038	49 (90.7%)	6 (75%)	0.189
CCB	10 (18.9%)	2 (20%)	0.933	10 (18.5%)	2 (25%)	0.665
C-I	18 (34%)	0	0.028	17 (31.5%)	1 (12.5%)	0.27
C-III	9 (17%)	1 (10%)	0.58	8 (14.8%)	2 (25%)	0.465
Co-morbidities						
CAD	5 (9.4%)	0	0.311	5 (9.3%)	0	1
CHF	14 (26.4%)	4 (40%)	0.383	13 (24.1%)	5 (62.5%)	0.025
DL	13 (24.5%)	2 (20%)	0.758	13 (24.1%)	2 (25%)	0.954
DM	5 (9.4%)	1 (10%)	0.955	4 (7.4%)	2 (25%)	0.116
HTN	19 (35.8%)	2 (20%)	0.389	18 (33.3%)	3 (37.5%)	0.816
Smoking	15 (28.3%)	4 (40%)	0.46	16 (29.6%)	3 (37.5%)	0.652
PVC site of origin						
Cusps	10 (18.8%)	2 (20%)	0.933	9 (16.7%)	3 (37.5%)	0.164
AMC	4 (7.5%)	0	-	4 (7.4%)	0	-
RVOT	30 (56.6%)	6 (60%)	0.842	32 (59.3%)	3 (37.5%)	0.279
MA	4 (7.5%)	0	-	4 (7.4%)	0	-
LV summit	2 (3.8%)	1 (10%)	-	2 (3.7%)	1 (12.5%)	-
LVOT	3 (5.6%)	1 (10%)	-	3 (5.6%)	1 (12.5%)	-
PVC transition zone						
V1	9 (17%)	1 (10%)	-	9 (16.7%)	1 (12.5%)	-
V2	8 (15.1%)	2 (20%)	-	8 (14.8%)	2 (25%)	-
V3	17 (32.1%)	7 (70%)	0.024	18 (33.3%)	5 (62.5%)	0.111
V4	19 (35.8%)	0	0.023	19 (35.2%)	0	0.044

*Continuous variables are shown as mean \pm 1 standard deviation. Categorical variables are shown as number (%).

ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin II receptor blockers **AMC:** aorto-mitral continuity **BB:** β -blockers **CAD:** coronary artery disease **CCB:** calcium channels blockers **CHF:** congestive heart failure **C-I:** class I anti-arrhythmic drug **C-III:** class III anti-arrhythmic drug **DL:** dyslipidemia **DM:** diabetes mellitus **HTN:** hypertension **LV:** left ventricle **LVEF:** left ventricular ejection fraction **LVOT:** left ventricular outflow tract **MA:** mitral annulus **PVC:** premature ventricular complexes **RVOT:** right ventricular outflow tract.

1-to-3 months follow-up (Table III). In contrast, a subgroup analysis of patients with RVOT SOO showed that transition zone at V4 had 100% success at 1-to-3 months follow-up, compared to 66.7% success in transition zone at < V4 (p -value = 0.019) (Table III).

Complications

Among the 63 patients undergoing the ablation procedure, three patients (4.7%) had major complications, two had cardiac tamponade that required urgent pericardiocentesis, and one patient had aortic dissection managed conservatively. No stroke, AV block or death were reported.

DISCUSSION

The most common site of origin of idiopathic PVCs is the RVOT followed by the LVOT. Less commonly PVCs may arise from other endocavity structures including papillary muscles, false tendons, moderator bands, valvular annuli, and from fascicular tissue especially the left posterior fascicle in young males [12,27-28].

The main mechanisms responsible for idiopathic outflow tachycardias are usually automaticity or delayed after depolarization (triggered activity), which are usually provoked by catecholamines, however they may sometimes be re-entrant because of anisotropic extensions of cardiomyocytes above the fibrous valvular annuli which hypothetically allow conduction slowing and unidirectional block [29].

The reported success rate of outflow tract PVCs ablation is 80% to 100% [30-31]. In our study, radiofrequency catheter ablation procedure targeting the predominant PVC morphology in patients with frequent, idiopathic outflow PVC was acutely successful in more than 84% of cases, and it decreased the PVC burden in more than 95% of patients in the first 24 hours post ablation. Success rates at 1-to-3 months of follow-up were also as high as 86% with more than 80% reduction of initial PVC burden and 89% with more than 50% reduction. In their retrospective multicenter cohort study that included 1185 patients, Latchamsetty *et al.* showed an acute procedural success of 84% and continued success at clinical follow-up during two years in 71% of cases [25].

The strongest predictor of 1-to-3 months success in our study was the absence of predominant PVC during the first 24 hours post ablation which is the same finding as the study done by Baser *et al.* [24]. On the other hand, Latchamsetty *et al.* found that RVOT SOO was the only predictor of both acute and long-term success [25]. However, in our study neither RVOT nor any other SOO was associated with outcome, while PVC transition from negative to positive at 12-lead ECG was significantly related. Despite the fact that RVOT SOO did not predict

TABLE III
ASSOCIATION BETWEEN ACUTE PROCEDURAL OUTCOME AND TRANSITION ZONE IN THE RVOT GROUP*

	< V4 N = 18	V4 N = 18	p value
Acute absence of PVC	12 (66.7%)	18 (100%)	0.019
Acute presence of PVC	6 (33.3%)	0	-

*Categorical variables are shown as number (%).

RVOT: right ventricular outflow tract

PVC: premature ventricular complexes

outcome in our study as previously reported, it is important to note that RVOT SOO with transition at V4 was associated with a 100% success rate.

A previous study showed that < V3 transition of precordial leads was diagnostic of LVOT origin with a sensitivity of 94.23% [32]. In our study, 95% of PVCs with QRS transition < V3 were of left-sided origin, and only 25% of those with transition at V3 were of left-sided origin.

To determine the origin of the PVC from the ECG morphology not only helps in deciding on the treatment approach, but also may help anticipate and improve outcome of ablation. Several previous reports have studied the significance of PVC transition in predicting the SOO [33-36], however, none have correlated PVC QRS transition to ablation outcome. Nevertheless, another ECG predictor was studied by Hachiya *et al.* who found that a peak deflection index* > 0.6 for outflow tract arrhythmias is associated with a higher rate of ablation failure which may indicate a non-endocardial (intramural or epicardial) site of origin [33]. In this study, PVC QRS transition from negative to positive at V3 was significantly associated with acute procedural failure (p -value 0.02); it also showed a clinical association with failure at 1-to-3 months of follow-up (62.5% vs 33.3%; p -value 0.1) despite no statistical significance due to the small number of patients. Moreover, the transition on V4 was significantly associated with procedural outcome showing a 100% success rate both acutely and on follow-up (p -value 0.02 and 0.04 respectively). A reasonable explanation could be the higher association of transition at V3 with left-sided or deep intramural origin, compared to transition at V4.

Acutely, complete elimination of the predominant PVC is not always possible, either because the SOO is at a risky proximity to a vital structure or cannot be reached, especially in the case of deep intramural and epicardial PVCs. PVCs originating from LV summit or tissue protected by surgical sutures may sometimes be also inaccessible. Ablating in the coronary veins, epicardial space, above the coronary cusps close to coro-

*Calculated by dividing the time from QRS onset to peak QRS deflection by total QRS duration.

nary ostia, and the posterior RVOT near the pulmonary valve, close to the course of the left main coronary artery may result in coronary artery injury [29]. In our study the ablation was not attempted in two cases because one was very close to the origin of the left main coronary artery and the second was close to the HIS bundle. In another patient the PVC was attempted but could not be eliminated due to its deep intramuscular origin.

Recurrence after successful ablation can be related to incomplete elimination, or to remodeling of the arrhythmogenic substrate or reconnection to exit sites. In our study, one case with complete initial elimination of the PVC had recurrence at three months, the origin of which was at the high postero-septal RVOT, QRS transition in this case was at V3. Another patient with significant reduction initially had recurrence at follow-up most probably due to insufficient lesions delivered at LV summit. In a study done by Baser *et al.*, PVCs recurred in approximately 15% of the cases in a series of patients with PVC-induced cardiomyopathy which resulted in recurrence of their cardiomyopathy [24]. A main finding was that PVC origin from the papillary muscles and pleomorphic PVC were associated with increased risk of recurrence. Similarly, Latchamsetty *et al.* also found that epicardial, papillary muscles, aortic cusps and pleomorphic PVCs were most associated with recurrence [25].

In our study, only outflow PVCs were included. Aortic cusps origin did not show an association with recurrence. Only one patient (1/8) with pleomorphic PVCs had recurrence of the predominant PVC at 1-to-3 months of follow-up with a 4% burden. Two cases had recurrence of PVCs with a non-predominant morphology with relatively low PVC burdens of 3% and 7%, not requiring re-intervention with significant improvement of symptoms. However, three months follow-up period is relatively short and that burden may further increase. The complication rate of 4.7% in this study was similar to the previously reported rates of 3 to 5.2% [25,28-40].

Limitations

This is a small single center series of patients and not all results could reach statistical significance. Larger studies are needed to evaluate this data. Follow-up results were determined according to 24-hour Holter monitoring which may be insufficient due to daily variability, however, this is the method used in common practice. The follow-up period was up to three months, further follow-up may be needed to determine long-term outcome.

CONCLUSION

Acute post procedural outcome within 12 hours of non-ischemic PVC ablation is a significant predictor of out-

come at one to three months post ablation with high sensitivity and positive predictive value. PVC transition at V4 is associated with a high procedural success while transition at V3 should alert the operator for a challenging procedure. Larger studies are needed to confirm these results, and to evaluate the relation between procedural outcome and PVC QRS transition zone in each PVC site of origin group.

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Disclosure

The protocol for this research project has been approved by a suitably constituted Ethics Committee of our institution and it conforms to the provisions of the Declaration of Helsinki. Institutional Review Board, Approval No. IM.BA.04

Conflicts of Interests

Authors declare no conflict of interests for this article.

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CARDIAC ARRHYTHMIAS

HIGH INCIDENCE OF STEAM POP FORMATION WITH THERAPY COOL FLEX RF ABLATION CATHETER

<http://www.lebanesemedicaljournal.org/articles/67-1/original7.pdf>

Mohammad EL BABA^{1*}, Wael AL JAROUDI^{2*}, Maria NADER¹, Marwan M. REFAAT¹, Maurice KHOURY¹
Bernard ABI SALEH¹

El Baba M, Al Jaroudi W, Nader M, Refaat MM, Khoury M, Abi Saleh B. High incidence of steam pop formation with Therapy Cool Flex RF ablation catheter. *J Med Liban* 2019; 67 (1):42-47.

ABSTRACT • Background: Open irrigation catheters have the advantage of delivering greater power without increasing the temperature of the catheter tip, which enables deeper and wider lesions without the formation of coagulum on catheters. The ThermoCool Celsius® radiofrequency (RF) ablation catheter is the most widely used open irrigated RF ablation catheter, while the Therapy™ Cool Flex™ is the first fully irrigated flexible tip catheter that has a laser cut electrode and conforms to tissue. We sought to evaluate the safety profile of the Cool Flex catheter during RF ablation as compared to the ThermoCool catheter. **Methods:** Patients who underwent RF ablation at the American University of Beirut Medical Center between July 2012 and October 2013 were retrospectively identified, and stratified depending on the type of catheter used during the procedure: Group 1, Therapy™ Cool Flex™ RF ablation catheter; and Group 2, ThermoCool Celsius® RF ablation catheter. The primary endpoints were: 1) Steam pop (detected by audible cue); and 2) pericardial effusion by intracardiac and transthoracic echocardiograms; and secondary endpoint was a composite of failed ablation, steam pop, effusion, tamponade or death. The study was approved by the Institutional Review Board and was set in according with the Declaration of Helsinki. **Results:** A total of 54 consecutive patients underwent RF ablation: 12 patients with the Therapy™ Cool Flex™ catheter (Group 1) and 42 patients with ThermoCool Celsius® catheter (Group 2). Patients in Group 1 were significantly older, had more coronary artery disease and heart failure and more likely to be on anticoagulation than those in Group 2. There was a significantly greater incidence of steam pop in the Therapy™ Cool Flex™ group (33.3% vs. 2.4%, $p < 0.05$) and more pericardial effusion (16.6% vs. 0%, $p < 0.05$) including one tamponade case that could not be resuscitated. After multivariate adjustment, Cool Flex catheter use was significantly associated with worse outcome (odds ratio 33.3 [3.30-336], $p = 0.003$). **Conclusion:** In patients undergoing irrigated RF ablation, the Therapy™ Cool Flex™ RF ablation catheter was significantly associated with an increase in the risk of steam pop formation and pericardial effusion as compared to the ThermoCool catheter group. Careful interpretation of the results is warranted given the small sample size and increased comorbidities in the Therapy™ Cool Flex™ group. A larger study is needed to confirm these results and further assess the safety of the catheter.

Keywords : ThermoCool catheter; Cool Flex; RF ablation; steam pop

INTRODUCTION

Radiofrequency (RF) catheter ablation is the therapy of choice for several cardiac arrhythmias. The aim of this technique is the creation of myocardial lesions of predictable size, thus minimizing the risk of complications [1].

Lesion size depends on the power delivered to the tissue and to the contact force applied by the catheter, but this is limited by the risk of local thrombus formation. The development of thrombi is directly related to the temperature reached at the catheter tip during the application of RF. Various cooling catheter tip systems have been developed to prevent the occurrence of local thrombus formation, allowing greater power delivery and, as a result, improving catheter efficiency and safety in lesion creation [2].

The two available methods for active electrode cooling to date are internal and external irrigation of the tip, the latter also called open irrigation. With the external system, fluid actively flows through holes arranged on the surface of the distal part of the electrode, reducing the overheating of the tissue-electrode interface [3]. As compared with standard RF ablation catheters, active electrode cooling allows the creation of larger lesions at sites with reduced blood flow and affords a lower incidence of thrombus formation [4].

In recent years a number of different electrode architectures for open-irrigated catheters have been developed, varying the tip dimensions, temperature sensors location and the number, size or distribution of the irrigation ports on the tip surface. However, there are limited data about whether electrode architecture differences have an impact on lesion generation and the occurrence of adverse events.

The aim of this analysis is to compare the safety of the diffuse irrigation of the Cool Flex catheter (Cool Flex catheter; St. Jude Medical) to the ThermoCool catheter (ThermoCool; Biosense Webster, Diamond Bar) that has six distal irrigation channels.

¹Division of Cardiovascular Medicine, American University of Beirut Medical Center, Beirut, Lebanon.

²Division of Cardiovascular Medicine, Clemenceau Medical Center, Beirut, Lebanon.

*Both authors contributed equally.

Corresponding author: *Bernard Abi Saleh, MD.* e-mail: ba47@aub.edu.lb

METHODS

We retrospectively looked at patients that underwent irrigated RF ablation procedures at the American University of Beirut Medical Center (AUBMC) between July 2012 and October 2013. The study was approved by the Institutional Review board of AUBMC and complied with the Declaration of Helsinki. The patient population was divided into two groups depending on the type of catheter used during the procedure: Therapy™ Cool Flex™ RF ablation catheter (Group 1) versus the ThermoCool Celsius® RF ablation catheter (Group 2).

RF energy using Therapy™ Cool Flex™ RF ablation catheter

In group 1, RF energy was delivered with the 4 mm tip fully irrigated Therapy™ Cool Flex™ RF ablation catheter (St Jude Medical, Sylmar, CA).

The catheter is open-irrigated with an irrigation flow at 17 cc per minute during RF energy application, the power delivered was between 15 watts and 30 watts with maximum temperature set at 40 degrees. RF delivery was interrupted in case of sudden rise in impedance.

RF energy using ThermoCool Celsius® RF ablation catheter

In group 2, RF energy was delivered with the 3.5 mm tip with six distal irrigation channels ThermoCool Celsius® RF ablation catheter (Biosense Webster, Waterloo, Belgium).

The catheter is open-irrigated with an irrigation flow at 30 cc per minute during RF energy application, the power delivered was between 20 watts and 40 watts with maximum temperature set at 42 degrees. RF delivery was interrupted in case of sudden rise in impedance.

Endpoints

The primary endpoints were:

- 1) Steam pop formation (detected by audible cue) &

- 2) Pericardial effusion by intracardiac and transthoracic echocardiograms.

Follow-up

All patients were monitored overnight on a telemetry unit after the procedure. Patients were followed in the outpatient clinic at 6 weeks post-ablation.

Statistical Analysis

Data distributions were first assessed for normality and for aberrancies.

Numerical data were expressed as mean \pm standard deviation, and compared using the Student's t test (normal distribution) or Wilcoxon test (skewed data).

Categorical data were expressed as percentage and frequency, and compared using the Pearson chi-square test.

A binary logistic regression analysis model was performed looking at predictors of poor outcomes. Because of limited number of events, a composite endpoint of failed procedure, steam pop formation, pericardial effusion, tamponade or death was used. Baseline covariates that were significantly different in the patients characteristics tables or thought to be clinically relevant were entered into the model. A multivariate model was performed adjusting for all univariates with p values < 0.10 .

All tests were 2-tailed, and a p value < 0.05 (set a priori) was considered statistically significant. All statistical analyses were carried out with SPSS Statistics version 22 (IBM, Inc., Armonk, NY).

RESULTS

Baseline characteristics of the study population are detailed in Table I. Patients in Group 1 were significantly older, had more coronary artery disease and heart failure and more likely to be on anticoagulation than those in Group 2.

TABLE I BASELINE CHARACTERISTICS STRATIFIED BY TYPE OF ABLATION CATHETER

	COOL FLEX Group 1 (n = 12)	THERMOCOOL Group 2 (n = 42)	p value
Age [years (sd)]	53.3 (16.2)	39.4 (19.1)	0.026
Body mass index [kg/m ² (sd)]	29.3 (6.7)	26.5 (4.9)	0.13
Male gender	6 (50%)	12 (28.6%)	0.17
Hypertension	5 (41.7%)	13 (31.0%)	0.49
Diabetes mellitus	3 (25.0%)	2 (4.8%)	0.033
Smoking history	7 (58.3%)	9 (21.4%)	0.014
Coronary artery disease	4 (33.3%)	5 (11.9%)	0.079
Coronary artery bypass graft	3 (25%)	1 (2.4%)	0.008
Congestive heart failure	8 (66.6%)	12 (28.5%)	0.016
Anticoagulation	6 (50%)	6 (14.3%)	0.009
Heparin usage	2 (16.6%)	29 (69%)	0.001
Antiplatelet	4 (33.3%)	10 (23.8%)	0.51

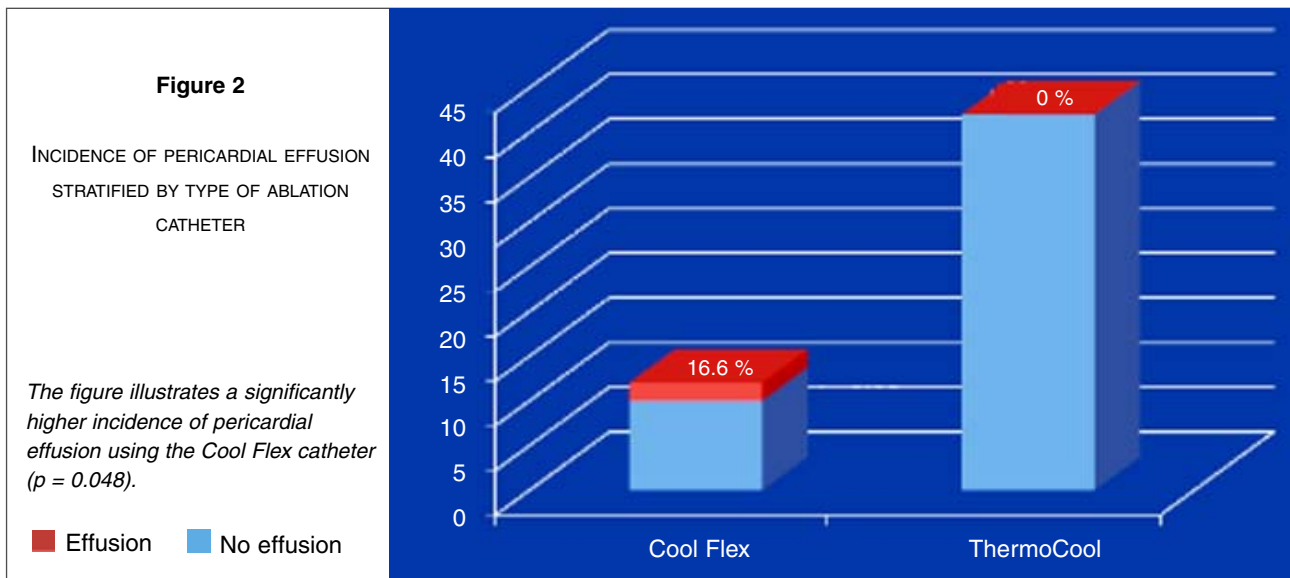
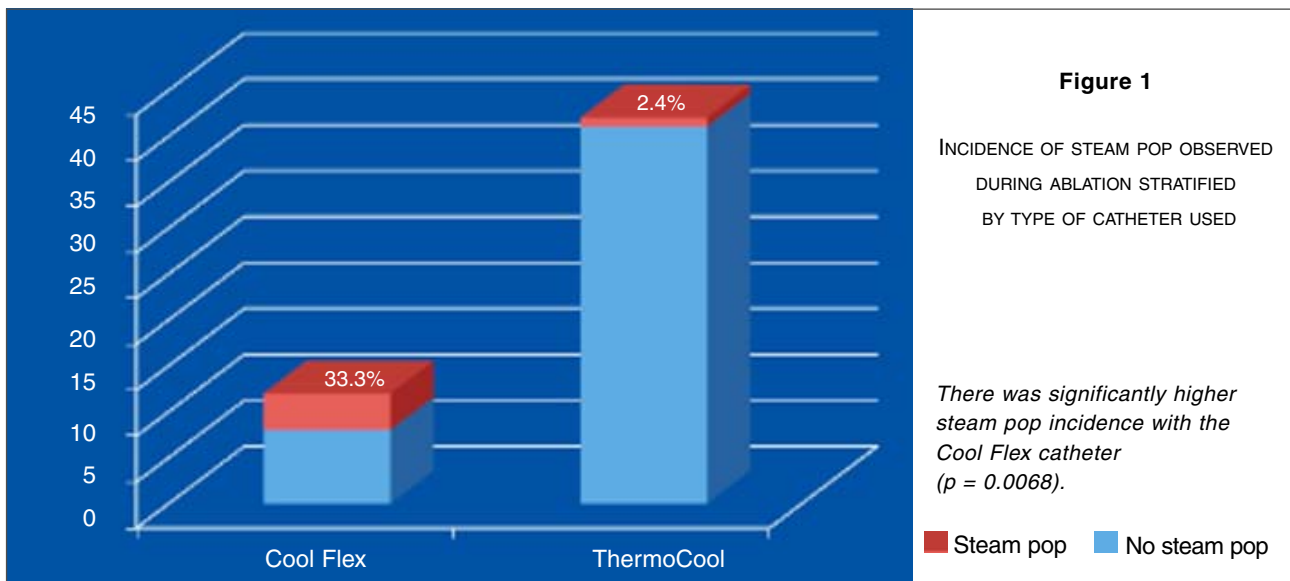


TABLE II
TYPES OF ARRHYTHMIA THAT WERE ABLATED STRATIFIED BY CHOICE OF CATHETER USED

	Cool Flex (Group 1) (n = 12)	ThermoCool (Group 2) (n = 42)	p value
Atrial flutter	1 (8.3%)	3 (7.1%)	0.89
Atrial fibrillation	5 (41.6%)	11 (26.1%)	0.30
Atrial tachycardia	0 (0%)	4 (9.5%)	0.27
Supraventricular tachycardia	1 (8.3%)	5 (11.9%)	0.73
Ventricular tachycardia	3 (25%)	6 (14.2%)	0.38
Premature ventricular complex	2 (16.6%)	15 (35.7%)	0.21
Wolf Parkinson White	1 (8.3%)	12 (28.5%)	0.15

There were 12 ablations with the Therapy™ Cool Flex™ catheter and 42 ablations with ThermoCool Celsius® catheter. There was a greater incidence of steam pop in the Therapy™ Cool Flex™ group (33.3% vs. 2.4%, $p < 0.05$) (Figure 1) along with higher incidence of pericardial effusion (16.6% vs. 0%, $p < 0.05$) (Figure 2).

One of the two patients that had a pericardial effusion went into tamponade and subsequently passed away on the table. This patient had severe ischemic cardiomyopathy with an ejection fraction at 10% and was undergoing a ventricular tachycardia (VT) ablation for VT storm.

There was no difference between the types of ablations done with the catheters (Table II). However, there were more right and left atrial ablations performed with the Thermocool catheter as compared with the Cool Flex

TABLE III
LOCATION OF ABLATION STRATIFIED BY TYPE OF CATHETER USED

	Cool Flex (Group 1) (n = 12)	ThermoCool (Group 2) (n = 42)	p value
Right atrium	6 (50%)	6 (14.2%)	0.009
Right ventricle	3 (25%)	11 (26.2%)	0.93
Left atrium	1 (8.3%)	21 (50%)	0.010
Left ventricle	2 (16.6%)	4 (9.5%)	0.48
Aortic cusps	0 (0%)	6 (14.2%)	0.16
Coronary sinus	1 (8.3%)	6 (14.2%)	0.59

catheter (Table III). In addition, more ablation procedures in Group 2 required heparin compared to the Group 1 procedures signaling that the Group 2 cases were mostly more complex arrhythmias cases.

The composite endpoint of failed procedure, steam pop, effusion, tamponade or death was significantly higher in the Cool Flex group (50% vs. 2.4%, $p < 0.0001$). After multivariate adjustment for baseline demographics, anticoagulation and location of ablation site, Cool Flex catheter use was significantly associated with worse outcomes (odds ratio 33.3 [3.30-336], $p = 0.003$).

DISCUSSION

In this study, we observed a significantly higher incidence of steam pop and pericardial effusion in the Cool Flex group, contrary to the study by Ramoul *et al.* [5] that was not able to show a statistical difference between the two catheters.

TABLE V
INDEPENDENT PREDICTORS OF POOR OUTCOMES POST ABLATION
(FAILED PROCEDURE, EFFUSION, STEAM POP, TAMPONADE OR DEATH)

Variable	Univariate		Multivariate	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age	1.03 [0.988-1.081]	0.148	–	–
Male	1.60 [0.32-8.01]	0.569	–	–
Body mass index	1.154 [0.989-1.347]	0.069	–	–
CAD	3.43 [0.664-17.7]	0.14	–	–
CHF	2.58 [0.51-12.97]	0.249	–	–
Diabetes	16.88 [2.15-132]	0.007	–	–
Anticoagulation	1.48 [0.249-8.79]	0.67	–	–
Heparin use	0.248 [0.043-1.42]	0.117	–	–
RA location	1.48 [0.25-8.80]	0.67	–	–
LA location	0.21 [0.023-1.85]	0.159	–	–
Cool Flex catheter	41.0 [4.18-402]	0.001	33.3 [3.30-336]	0.003

CAD: coronary artery disease CHF: congestive heart failure
RA: right atrium LA: left atrium

TABLE IV
OUTCOMES STRATIFIED BY TYPE OF CATHETER USED

	Cool Flex (Group 1) (n = 12)	ThermoCool (Group 2) (n = 42)	p value
Failed procedure	1 (8.3%)	0 (0.0%)	0.059
Steam pop	4 (33.3%)	1 (2.4%)	0.001
Pericardial effusion	2 (16.7%)	0 (0.0%)	0.007
Tamponade	1 (8.3%)	0 (0.0%)	0.059
Death	1 (8.3%)	0 (0.0%)	0.059

Knowing that the Cool Flex catheter was used as per the recommendation of the company with maximum power of 30 watts and max temperature set at 40 degrees compared to the ThermoCool group whereby a power of 40 watts was delivered for some cases with max temperature of 42 degrees. The Ramoul *et al.* study [5] was done on right atrial flutters only but our study included several types of ablation procedures. The risk of causing a pericardial effusion during the ablation of the cavotricuspid isthmus is low given the thickness of the isthmus and this could have been the reason why there was no pericardial effusion in the Ramoul *et al.* study [5].

Experimental studies have demonstrated that at a given electrode size and electrode-tissue contact force, the delivered power and the resulting rise in tissue temperatures are the important parameters that determine the radiofrequency lesion size [6]. An open-irrigated catheter (by cooling the RF delivering catheter electrode tip) allows delivery of higher RF power to the myocardial tissue (even at atrial sites of low blood flow), enabling deeper, and larger lesions [7].

In addition, this external irrigation also reduces the risk of char and thrombus formation at the interface between electrode tip and tissue and reduces the occurrence of steam pops [8], therefore, open-irrigated catheters are the state-of-the-art technology for radiofrequency ablation. Newer irrigated catheters aim to improve the irrigation efficacy. The Cool Flex catheter provide a theoretical better irrigation flow by providing more outflows around the whole tip [8,9].

A study conducted by J. Moreno *et al.* compared the newer catheters ThermoCool SF, Cool Flex and Blazer™ Open-Irrigated, with the standard ThermoCool catheter [10]. This study showed that the newer catheters showed lower temperature readings compared with the ThermoCool. No major efficacy or safety differences were found at tangential applications; however, at perpendicular applications: the Cool Flex created smaller lesions than SF and readily induced steam pops at 50 W without temperature control.

The success of radiofrequency ablation is entirely dependent on full transmural lesion formation [11]. If too much energy is applied, there can be serious complications like perforation of the atrium, tamponade or embolisms [12]. Of all the factors that influence lesion formation, local catheter endocardial contact geometry (penetration depth and incident angle) is the least well controlled due to a lack of soft tissue contrast in the fluoroscopy images used to track catheter location.

There is a large amount of data illustrating the important effect that catheter/endocardial contact has on electrical coupling [13], naturally occurring cooling, heat accumulation, maximum temperature, the transient response of each, and the resulting lesion formation [11, 13]. In addition, preliminary studies have shown that there are significant differences in initial measured electrical impedance depending on catheter/tissue angle even at the same penetration depth [14]. Despite this, and the fact that unknown endocardial contact geometry is a well known limitation of the procedure [15], how lesion formation is affected by the incidence angle of the catheter requires further elucidation.

Catheter angle had a very large effect on lesion volume with up to a two-fold difference in size between the angle extremes. As the angle between the catheter and the tissue became more acute for a given depth, more electrode surface was in contact with myocardium. Thus, this easily explains a larger lesion volume without increasing lesion depth. However, lesion depth also increased greatly for very acute angles, due to a larger heating surface having less curvature directly under the electrode. It is clear that catheter contact geometry (not just penetration depth) is important not only when it comes to the ultimate lesion dimensions but also to the T_{max} induced in the tissue. At greater penetration depths, catheter angle played an even more significant role in lesion formation parameters with the more acute angles (particularly 15°) having the greatest depths, widths and volumes [16].

Conventional irrigation catheters have theoretical limitations with respect to the efficiency of irrigation.

Indeed, on a planar tissue surface, irrigation holes positioned at the interface between the catheter and the tissue surface are obstructed by the tissue itself and most of the irrigation will be delivered through the unobstructed holes into the blood pool. A more 'intelligent' design of irrigation, i.e. mainly distributed to the tissue-electrode interface during RF application with parallel positioning of the catheter, has theoretical benefits, as does internal global irrigation. One of the problems with conventional irrigation is unequal cooling of the catheter tip and the tissue, such that lesion size and growth are dependent upon catheter-tip orientation relative to the tissue [16].

The multiple variables that effect power delivery and lesion growth (contact force, current density, edge effects, active, and passive cooling of the tissue) mean that in clinical practice the electrophysiologist only has the vaguest of notions as to how a lesion is being formed, although catheters for direct lesion assessment are being developed [17]. It is this variability that can result in complications from RF catheter ablation including steam pops, which can result in perforation and cardiac tamponade and may also lead to inadequate lesion formation resulting in either procedural failure or recurrence of arrhythmia due to temporary, sublethal myocardial damage.

Furthermore, the Cool Flex catheter has a specific design with a fully irrigated and flexible tip. However, the theoretical benefits of this catheter-tip design of uniform cooling and hence more predictable lesion formation did not result in demonstrable clinical safety in the present study. One of the reasons why this catheter-design did not translate into clinical safety could be the ridged shaft with flat wiring system compared to the spiral wiring system of the ThermoCool catheter. This is of a considerable importance in a beating heart as the catheter body has to react to the heart beat during RF application. In addition, the distal part of the catheter, particularly between the electrodes, does not bend the fact that negates the benefit of the flexible tip. In details, the Cool Flex catheter has a straight end that starts 1 cm before the proximal electrodes whereas the ThermoCool catheter bends all the way till the distal electrode which decreases the axial force to the tissue (Figure 3).

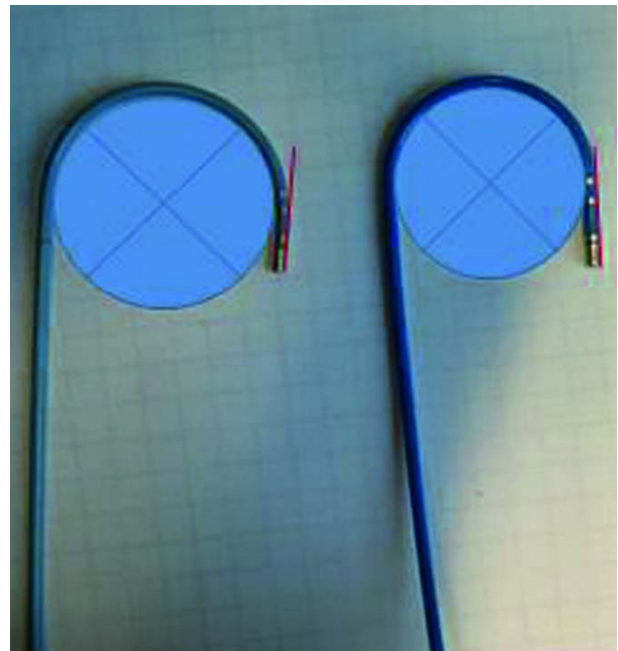


Figure 3
Comparison of Cool Flex and ThermoCool curvatures

Study limitations

This is a retrospective study from a single tertiary center and of small sample size with likely referral and selection bias. However, having a larger study population might have diluted the differences between the catheters. In addition, we could not enroll more patients in Group 1 because the use of this catheter has decreased significantly after observing the complications associated with it. Finally, as this study was performed in the clinical setting utilizing the Cool Flex catheter and the conventional ThermoCool catheter, no estimation of intramural tissue temperature, thrombus formation or contact force on the electrode-tissue interface was possible.

CONCLUSION

The current study showed that in patients undergoing irrigated RF ablation the Therapy™ Cool Flex™ RF ablation catheter significantly increases the risk of steam pop formation and increases the risk of pericardial effusion. A large and randomized trial is needed to confirm our findings.

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POSTFACE

<http://www.lebanesemedicaljournal.org/articles/67-1/postface.pdf>

This special issue dedicated to cardiac arrhythmias includes data on cardiac implantable electronic devices (CIEDs), arrhythmias ablation, atrial fibrillation (AF) epidemiology... which were missing until now in our country, even though Lebanon is a European Society of Cardiology (ESC) member country. Unfortunately, the number of patients included remains relatively low, the majority being recruited by only one tertiary hospital, hence the need to conduct national multicentre studies and registries.

Three medical papers are technical. In the first, the authors conclude that the Therapy™ Cool Flex™ RF ablation catheter, in a study of 54 patients, was significantly associated with an increase in the risk of steam pops formation and pericardial effusion compared to ThermoCool® catheter group [1]. The second evaluates the ECG predictors of outcome after radiofrequency catheter ablation of frequent non-ischemic premature ventricular contractions (PVCs), in a retrospective trial of 63 patients, showing that the acute occurrence of non-ischemic PVCs within 12 hours is a predictor of adverse outcome, and PVC transition from negative to positive at V3 instead of V4 might be predictive of failed ablation [2]. In the third paper, the authors demonstrate that the Evolution mechanical dilator sheath, used in 43 patients, is a useful and safe tool as first line management in transvenous lead extraction, with the complete success achieved in 88.3% of cases [3].

The epidemiology of AF reported in a registry was a single center experience of 103 patients, from 2015 to 2017, including gender, etiology, paroxysmal or permanent arrhythmia, associated comorbidities: diabetes mellitus (DM), hypertension, smoking, coronary artery disease (CAD), congestive heart failure (CHF). This publication reveals that a large proportion of patients had a CHADS2 (about 30%) or CHA2DS2-VASC (about 60%) higher than 2, with approximately 15% of this high-risk population not treated with oral anticoagulation [4].

The association between DM, AF and ventricular arrhythmias (VAs) was related in a review article in collaboration between the American University of Beirut (AUB), Emory University School of Medicine, Atlanta, and Hamad Medical Corporation & Weill Cornell Medicine in Doha, Qatar. Hyperglycemia induces oxidative stress in animal studies resulting in myocardial injury and cell ischemia, and formation of advanced glycosylation end products invading the myocardium with diabetic cardiomyopathy as a consequence, both predisposing to AF. On another hand, patients with DM have a significantly higher incidence of T-wave alternans and a vulnerable diabetic myocardium, leading to the occurrence of VAs. The authors focus on primary prevention of DM, CAD, and atherosclerosis [5].

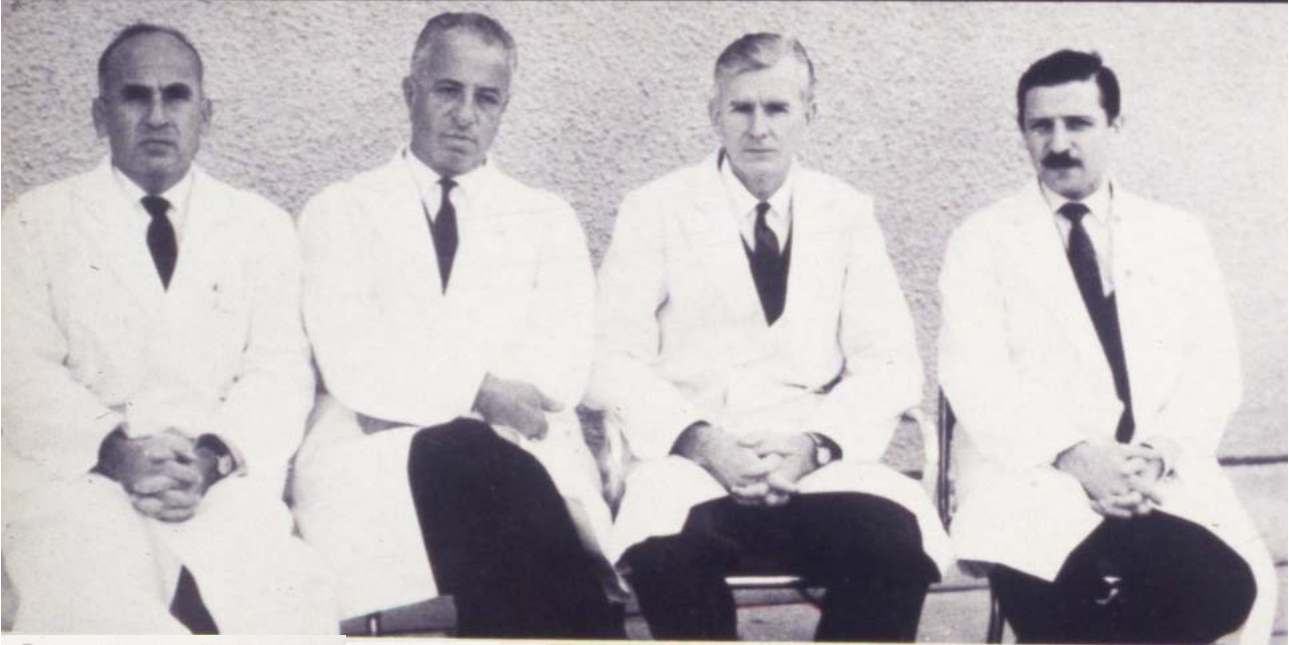
Two multicenter epidemiologic studies related the evolution, during the last years, of the CIEDs and ablation procedures in Lebanon. The first reveals that CIED implants expanded significantly over the past years, mainly the dual double chamber pacemakers, but also CRT-Ds, dual chamber and single chamber ICDs; total pacemakers increased from 730 in 2013 to 983 in 2017, and total ICDs from 546 to 673 during the same period [6]. The second, also reported a significant increase in cardiac ablation procedures from 20 to 60 in 2010, to around 100 in 2013, and to 350 in 2017. This growth in cardiac implantations and arrhythmias ablations results from the increase of the number of cardiac electrophysiologists and the specialized electrophysiology units in tertiary hospitals [7].

The last paper, in collaboration between AUB and the University of Pittsburg, Pennsylvania, compared the use of robotic remote catheter navigation (RCN) in AF ablation by radiofrequency (70 patients), to manual control navigation (MCN). RCN was associated with significantly increased laboratory and ablation procedures but decreased fluoroscopy times, and mainly a higher rate of sinus rhythm maintenance (70% vs 47%) at two years [8].

Finally, I congratulate all the colleagues and mainly the corresponding author, Prof. Marwan Refaat, for all the efforts made to achieve the writing of this particular issue, and I sincerely encourage them to continue in the same way mainly by conducting national multicenter trials and registries, for the best of our country.

Roland KASSAB, MD*
Editorial Board, LMJ

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- * Division of Cardiology, Saint-Joseph University - Hôtel-Dieu de France University Hospital, Beirut, Lebanon.



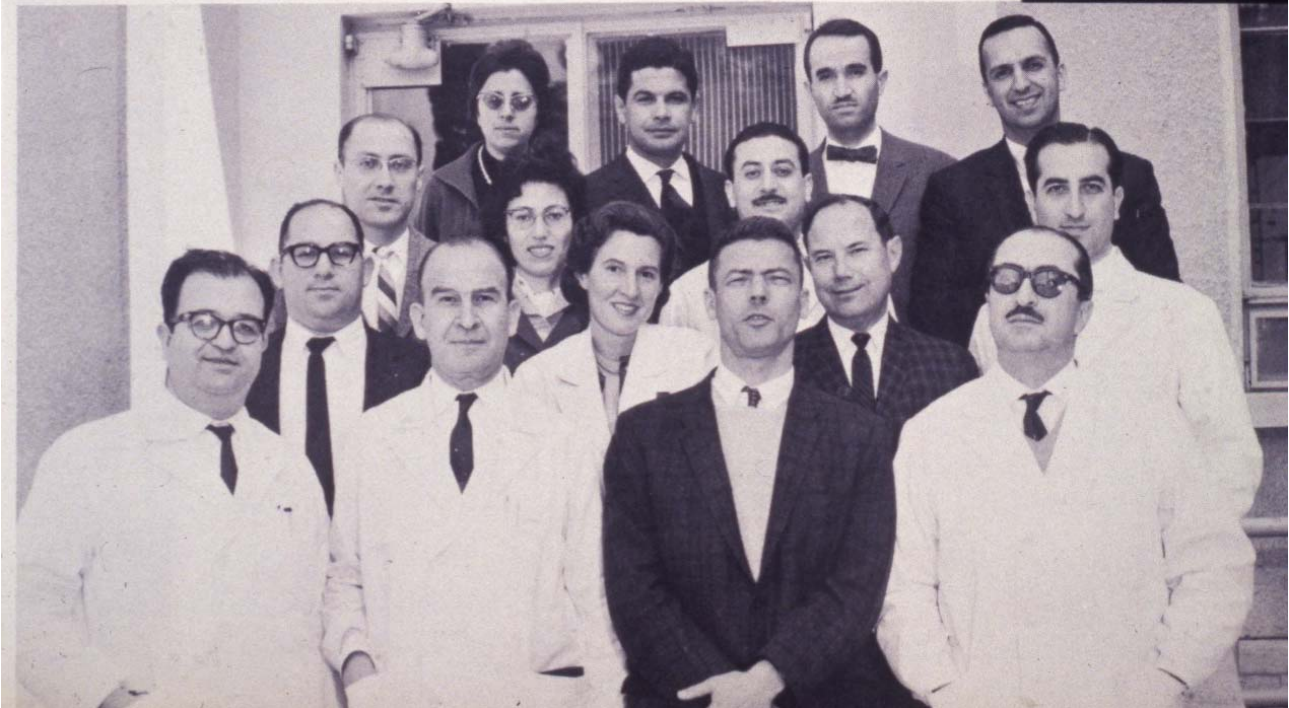
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GUIDELINES

BRUCELLOSIS PREVENTION AND CONTROL IN THE MEDITERRANEAN & MIDDLE EAST REGIONS – A GUIDANCE TOWARDS APPROACHING THE TARGETS

<http://www.lebanesemedicaljournal.org/articles/67-1/guidelines1.pdf>

Aristarchos SEIMENIS^{1*}, George F. ARAJ^{2*}, Ignacio MORIYÓN³, Darem TABBAA⁴

Seimenis A, Araj GF, Moriyón I, Tabbaa D. Brucellosis prevention and control in the Mediterranean and the Middle East regions - A guidance towards approaching the targets. *J Med Liban* 2019; 67 (1): 52-61.

ABSTRACT-OBJECTIVES: Brucellosis remains one of the major zoonotic infections creating significant multidimensional medical, public health, social and economic problems to more than 120 countries, especially the developing ones, throughout the world. Moreover, most *Brucella* spp. are listed as biosecurity/bioterror pathogen by the CDC. Among the 13 identified species, *B. melitensis* poses the highest risk for humans in most countries. This is due to contact with sick livestock or ingestion of raw milk, cream, and soft cheese from infected sheep and goats, which constitute the main reservoir of infection. Facing this zoonosis challenge imparts major attention on national authorities to shoulder responsibility towards building successful prevention and control programs. In any country or geographical zone, the effective establishment and implementation of such programs require tackling several factors including: 1) Awareness and public health education about the disease; 2) Diagnostic capacity and facilities for adequate and reliable identification of cases, avoiding misdiagnosis and underreporting in both public and animal health sectors; 3) Vaccination strategies and programs; 4) Intersectoral and interagency coordination; 5) Intersectoral epidemiological surveillance systems; 6) Political commitment and financial support and 7) Liaison with international organizations such as FAO, WHO and WOAAH (OIE), that can provide valuable technical support, expertise sharing, capacity building and funds mobilization. These factors were encountered and addressed through an important technical level's contribution led by the WHO-Mediterranean Zoonoses Control Centre during the implementation of two "Pilot Brucellosis Epidemiological Surveillance Projects in the Public Health and Animal Health Sectors in Syria and Jordan". These endeavors revealed a dire need for making available information adapted to reality and addressing appropriate approaches for *Brucella* prevention and control. The present document is based on the long experience of the authors in this field and has been warranted to address the aforementioned issues and factors in a clear, concise, well cross-checked, practical and "easy-to-handle" guidance, applicable before and during brucellosis control activities.

Keywords : zoonoses; brucellosis; epidemiology; prevention/control; diagnosis; one health

¹WHO-Mediterranean Zoonoses Control Centre, Athens, Greece.

²Clinical Microbiology Division, Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center, Beirut, Lebanon.

³Institute for Tropical Health, Department of Microbiology and Parasitology, University of Navarra, Pamplona, Spain.

⁴Department of Public Health, Faculty of Veterinary Medicine, University of Hama, Syria.

*Corresponding authors: *Aristarchos Seimenis, DVM, PhD*
George F. Araj, PhD, D(ABMM), FAAM
e-mails: seimenisaris@gmail.com / garaj@aub.edu.lb

ABBREVIATIONS

ELISA	Enzyme-linked Immunosorbent Assay
iELISA/cELISA	Indirect ELISA/Competitive ELISA
CDC	Centres for Disease Control and Prevention
FAO/UN	Food and Agriculture Organization of the United Nations
FBDs	Foodborne Diseases
FPA	Fluorescent Polarisation Assay
MME	Mediterranean and Middle East
MMER	Mediterranean and Middle East Regions
MZCC	Mediterranean Zoonoses Control Centre
MZCP	Mediterranean Zoonoses Control Programme
NMC	Northern Mediterranean Countries
	Countries in the Northern Mediterranean littoral: France, Greece, Italy, Portugal, Spain.
OIE	World Organization of Animal Health
OIE-RRME	Office International des Epizooties - Regional Representation for the Middle East Member Countries: Afghanistan, Bahrain, Egypt, Iraq, Iran, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Sudan, Syria, Turkey, United Arab Emirates, Yemen.
SEMER	Southern and Eastern Mediterranean Region Countries considered in the Southern and Eastern Mediterranean littoral: Algeria, Cyprus, Egypt, Lebanon, Libya, Morocco, Syria, Tunisia, Turkey.
SMMER	South Mediterranean and Middle East Regions Countries considered in the SMMER: Bahrain, Egypt, Jordan, Iraq, Kuwait, Lebanon, Libya, Morocco, Oman (Sultanate of), Palestine, Qatar, Saudi Arabia (Kingdom of), Sudan, Syria, Tunisia, United Arab Emirates, Yemen.
WHO	World Health Organization
WHO-EMRO	WHO-Eastern Mediterranean Regional
WOAH-OIE	World Organization of Animal Health-OIE.

DISCLAIMER

The views expressed in this document are solely the responsibility of the named authors which do not necessarily represent the views, decisions or policies of the institutions they represent.

INTRODUCTION

Brucellosis remains a major zoonotic disease, tolling both the human and animal sectors at different levels worldwide. In animals, it affects cattle, buffaloes, sheep, goats, swine, camels, certain marine mammals, and other animals leading to abortions, reduced fertility up to sterility in infected animals. Rural and urban populations are at a continuous risk of contracting brucellosis. Beside its

important medical and social impact, it creates a heavy economic burden both at the family and national levels.

Often, this disease, lacking pathognomonic symptoms, can be easily confused with other febrile conditions especially in tropical countries where it might be misdiagnosed as drug-resistant malaria and typhoid fever.

In many developed countries, this disease has been controlled or eliminated. This has been achieved through mass media awareness campaigns, systematic epidemiological surveillance, mass vaccinations, test-and-slaughter policies, compensation of farmers, and other incentives. Such applied strategies in the animal sector lead to a successful reduction of cases in humans. In most developing countries such as the South Mediterranean and the Middle East (SMME), brucellosis often remains unidentified and under-reported. Moreover, diagnosis occurs mostly at an advanced stage entailing prolonged and chronic illness and disability [1-5].

EPIDEMIOLOGY

Brucellosis prevalence and incidence in animals and humans vary among countries in the MME regions. First, those of the Northern Mediterranean littoral (NMC) where efficient control programs have been concluded (France) or are in evident progress, e.g. Spain, Portugal, Italy and Greece, showed reflection on the decrease of

human cases. Second, countries of the Southern and Eastern littoral together with those of the Middle East (SMMER) such as Jordan, Oman, Syria and Turkey, where nationwide free vaccination programs have been implemented for the owners, have had different results in terms of progress and success. In other countries in the same area, e.g. Egypt, vaccination is usually not compulsory and owners of infected slaughtered animals/flocks are not usually compensated. Such epidemiological differences among the two regions can be ascribed to the efficiency of control, and the level of social awareness in association with public health education activities.

Vaccination efforts in animals are also an important factor in controlling the disease in both animals and humans. Many countries succeeded in reducing brucellosis prevalence in cattle, but little success was met with sheep and goats' vaccination. This is due, among other factors, to serious difficulties encountered by the veterinary services in identifying, vaccinating, and monitoring infected flocks as well as in controlling their movements at national and transboundary levels. Such a situation triggered the FAO/UN to undertake in 2012-2014 the initiative for the development of a "Stepwise Approach for Progressive Control of Brucellosis in Livestock-Principles, Strategies, Stages and Tools", aiming at the progressive control of brucellosis in accordance to areas and/or zones [6-8].

Table I includes brucellosis cases in humans officially

TABLE I
REPORTED CASES OF HUMAN BRUCELLOSIS IN SELECTED MEDITERRANEAN AND MIDDLE EAST COUNTRIES OVER TEN YEARS*

COUNTRY	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	TOTAL
Algeria	8032	7812	7733	5056	6378	8445	4445	5298	4170	6132	63501
Cyprus	2	0	0	0	0	0	0	0	0	0	2
Egypt	5209	5212	5120	5300	3969	3641	3790	4447	3951	3756	44395
Greece	331	284	153	339	114	97	100	123	159	135	1835
France	39	30	14	21	23	20	11	21	9	**	188
Italy	632	318	179	163	167	171	166	184	137	14	2131
Jordan	132	132	217	111	130	129	155	96	158	273	1533
Lebanon	175	240	265	157	333	303	134	134	189	252	2182
Oman	113	69	88	**	70	154	126	148	192	217	1177
Portugal	170	95	75	81	81	86	85	47	35	62	817
Palestine Territory	126	94	221	199	195	206	179	148	244	401	2013
Qatar	26	35	**	22	42	25	31	24	53	0	258
Spain	328	324	246	160	152	106	100	83	103	79	1681
Syria	26739	29341	39838	25315	19213	3520	2860	1452	9273	10994	168545
Tunisia	284	460	514	285	265	371	368	278	140	409	3374
Turkey	14644	10790	11803	9818	9324	7658	7177	6759	7225	4475	89673
GRAND TOTAL											383305

* OIE data base: *zoonoses in humans* and EFSA-EU-EFSA Journal 2015; 13: 4329. ** Data not available
Available at: www.oie.int/wahis2/wash/action7en.php / www.efsa.europa.eu/efsajournal

reported in most Mediterranean, and Middle East (MME) countries during a decade, while Figure 1 reflects the correlation of the infection diagnosed per millions of inhabitants per country. The improved epidemiological situation among Northern Mediterranean countries (NMC) is due to decades of efficient control programs campaigns, and public health education. Among the SMMER countries, however, the number of cases declared on a yearly basis, in no way reflects the real epidemiological situation. This could be based upon information of ambiguous significance and origin associated with the collapse of prevention/control programs due to conflicts (e.g. Syria) or stagnant situation related to administration weaknesses. Regardless of the reasons, the existence of such cases should constitute the impulse for establishing longstanding strategic control plans. In Jordan, the number of cases reported during the same period generally remained steady [9-19].

Besides the fact that brucellosis is eclipsed as a neglected tropical disease in many countries in the Middle East and the developing world, several other hampering conditions should be considered by national competent authorities in the endeavor towards the prevention and control of this disease. These include entrenched behaviors fostered by ignorance, sociocultural and sociopolitical behaviors together with lack of intersectoral collaboration and coordination, weak national infrastructures, lack of public health education and public awareness. Such and other relevant determinants should be considered by national competent authorities as well as by international organizations as of critical importance towards development progress [20-23].

Epidemiological surveillance

Epidemiological surveillance (ES) is a tool used to detect and monitor epidemics and public health emergencies, and constitutes an essential information system for action towards prevention and control. This is needed to estimate the magnitude of the problem in the human population (morbidity, mortality, case fatality, disability, trends of the infection), identify high risk population(s) and risk factors (e.g. fresh cheese, raw milk, contact with animals, etc.), and improve the detection level and treatment of patients. In animals, the detection of outbreaks, as well as the monitoring of changes in *Brucella* species/biovars in a given population and/or area are necessary for the success of the activity.

The aforementioned should go together with establishing a vertical and horizontal communication and planning within and in-between public health and animal health sectors. This should go together with developing a functional database for regular intercommunications among all sectors and agencies that are directly involved in brucellosis prevention and control [24-26].

In the Middle East, a noteworthy example of such endeavor is the “*WHO-MZCC Pilot Brucellosis Epidemiological Surveillance Projects in Syria and Jordan 2003-2006*”. Requests from the Syrian and Jordan Ministries of Health and Agriculture were addressed to the WHO-MZCC in 2002 and 2004, respectively, for technical assistance in the improvement of their human and animal brucellosis epidemiological surveillance systems. Both projects had perspectives to integrate, in this specific field, the public health and animal health sectors in order to promote the use of data and information system standards to advance the development of an efficient, in-

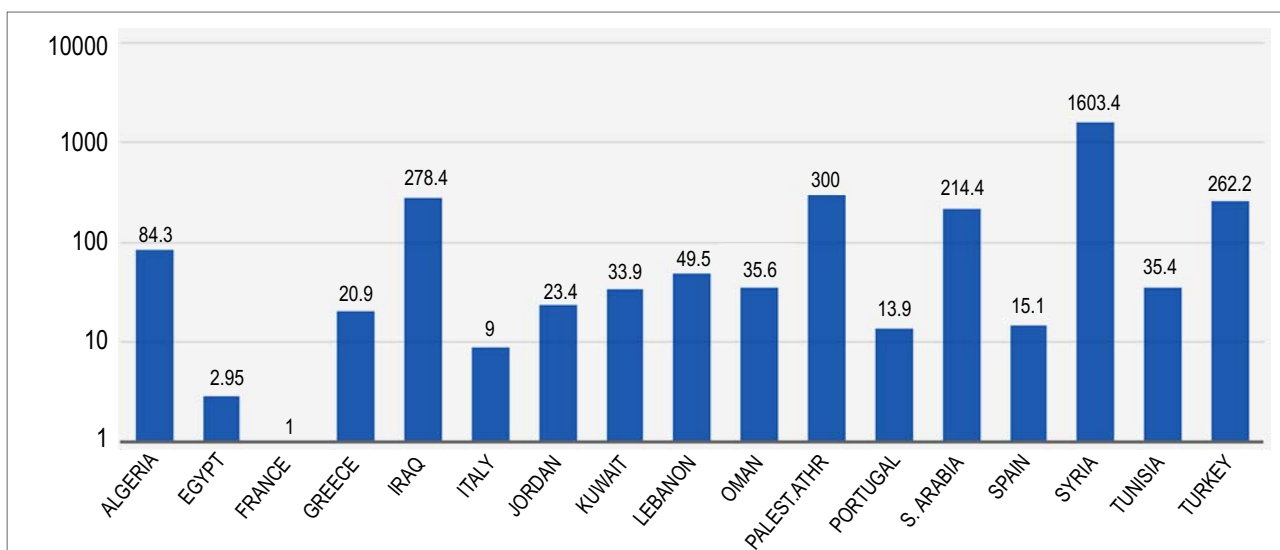


Figure 1. Brucellosis cases in humans per million of population in selected Mediterranean and Middle East countries (Adapted by J.W. Al Ramahi, *Infect.Dis.Medicine.Soc.Tun.Path.Infect.*, 2012.) www.infectiologie.org.tn/pdf/.../j_wadi.pdf

tegrated and interoperable brucellosis surveillance system at national, provincial and local levels. The reorganisation of the brucellosis diagnosis central laboratories in both countries, together with manpower training, and purchase of necessary equipment and other materials were included among the undertaken measures. At the conclusion of the projects, the national authorities reached the main target, i.e. the horizontal and vertical intercommunication of the information gathered and analyzed by the newly implemented surveillance system [23].

LABORATORY DIAGNOSIS OF BRUCELLOSIS

Human brucellosis can present with a variety of manifestations, making the diagnosis unreachable on mere clinical grounds. Laboratory support is therefore essential. A brief overview of the main laboratory diagnostic procedures used for the detection of infections in humans and animals are described.

Laboratory diagnosis in humans

Isolation of *Brucella* spp. from patients' clinical specimens by culture provides the definitive diagnosis. Culture, however, takes a long time, and is associated with a low or variable recovery rate (40-80%) warranting serologic tests to be performed, almost always, in combination. Among different serology tests, the most commonly used are: Slide Agglutination test, Standard Tube Agglutination test (SAT), Rose Bengal test (RBT), 2-Mercaptoethanol test (2ME-in few countries), indirect Coombs test, indirect Enzyme-linked Immunosorbent Assay (iELISA) and Brucellacapt test.

All these tests can provide positive results in patients with acute or subacute brucellosis, where IgM is present. However, complicated cases such as chronic, neurological, and focal brucellosis, can be missed by slide tests and SAT. In fact, in these cases IgG, incomplete, non-agglutinating or blocking antibodies are likely to be present, which requires the use of specific and highly sensitive tests, namely indirect Coombs, Brucellacapt or ELISA, that are able to detect these antibodies and help in the diagnosis.

Therefore, and for practical reasons, it is advisable to deploy a combination of SAT with either indirect Coombs, Brucellacapt or ELISA to avoid missing a diagnosis. Of note, the need to interpret serology results with the history and clinical status of the patient is of high importance, since antibodies may persist despite of treatment and cure, and other illnesses could fall within the differential diagnosis.

RBT is appropriate in small and understaffed laboratories, as it possesses high sensitivity. However, while it is easy to observe a positive RBT agglutination in acute

stages, training is required to interpret the thinner agglutination reaction that appears in long evolution cases [27-31].

Laboratory diagnosis in animals

In animals, isolation of the agent in culture is also the only conclusive technique. However, serology is the most common and practical tool used. Serological tests must be interpreted in accordance with the disease history and vaccination status to avoid false positive reactions of the herd/flock.

Serological diagnosis in bovines includes RBT or other Buffered Plate Agglutination tests, Complement Fixation test (CFT), indirect ELISA (iELISA) and Fluorescence Polarization Assay (FPA). They are suitable for screening herds and individual animals. The milk-ring test can be used on bulk milk samples for screening and monitoring dairy cattle. The iELISA should also be useful in bulk milk but the conditions of use remain to be established. The SAT should be avoided due to reduced sensitivity and specificity [32].

In sheep and goats the RBT and CFT should always be used in combination and are recommended for screening flocks and individual animals, though both have low specificity when sera from Rev.1 subcutaneously vaccinated sheep and goats are tested. This drawback is significantly reduced if conjunctival (i.e. ocular instillation) vaccination is adopted due to the reduced level and the shorter duration of the resulting serological response. Between iELISA and competitive ELISA tests, the former one is more sensitive, even more so than both RBT and CFT. None however, can differentiate between infected animals and recently vaccinated ones. Moreover, there is still a need for further experience to be accumulated in the field in order to fully validate the use of ELISA's in sheep and goats, as the cut-offs suggested by manufacturers need to be reevaluated under the specific epidemiological conditions of most SMMER's countries.

Other non-widely used tests for financial reasons are: Gel Precipitation test, Immune Capture test and FPA. Brucellin skin allergic test is useful for screening unvaccinated herds and flocks [33-36].

PREVENTION AND CONTROL IN SMMER

Effective prevention and control programs necessitate certain essential requirements and key elements to ensure long-term management of complex projects including: human resources development through capacity building, training of public health, and animal health staff in all aspects of brucellosis, public health education towards community awareness and participation, motivation of breeders' collaboration, promotion of a cross-sectoral co-

ordinated cooperation of all competent sectors, especially the public health and animal health sectors.

The countries of the South Mediterranean and Middle East regions (SMMER) share many common epidemiological, socioeconomic, structural and other characteristics such as breeding of small ruminants, food and behavioral habits, mentalities, beliefs and education. Therefore, effective long-term prevention and control programs planned to be implemented in the SMMER should respect and take into consideration, with certain exceptions, the aforementioned characteristics. Moreover, the strategic approach for a successful program should address several factors encompassed in the text to follow [10, 37-44].

Design of control plans

The planned strategy should take into consideration several factors including understanding of local and regional variations in animal husbandry practices, epidemiological patterns of the disease, the level of infrastructure support, cross-sectoral brucellosis epidemiological surveillance and coordination, social customs, and community awareness, among others.

Since there is no available efficient brucellosis vaccine for humans, prevention of the infection relies on its control in the animal reservoir. Protecting public health calls for the adoption of long-term programs and strategies related to both the animal and human populations and encompassing national competent agencies and services. In the developing countries such as the SMMER, among other obstacles, data about the real prevalence of brucellosis remains scarce; hence control strategies should be grounded on the following perspectives:

- Establishment of an efficiently-operating intersectoral epidemiological surveillance system.
- Introduction, as much as possible, of extensive and effective vaccination programs for susceptible livestock (bovine, sheep, goats and, where appropriate, buffaloes and camels).
- The strategy of vaccination should take into consideration the mostly nomadic, and transboundary type of sheep and goat-rearing prevailing in the SMMER.
- Animal identification, where feasible, is strongly recommended, otherwise, differentiation between vaccinated and non-vaccinated animals will be almost impossible.
- The only suitable vaccines available at present, despite their known drawbacks, are S19 in bovine and Rev1 in sheep and goats.
- The RB 51 vaccine is recommended for cattle only. However, although it doesn't confer post-vaccination antibody titers in RBT and CFT, it interferes in ELISAs assays. Furthermore, it seems to be associ-

ated with paradoxical outcomes in terms of safety, causing abortions, as well as low level of conferred immunity. Consequently, its use as a strategic immunization tool remains under discussion [37]. Nevertheless, RB51 complementary use to S19 vaccine has been reported in some studies [40,42].

Vaccination process

- During the first year of sheep and goat vaccination programme, mass conjunctival vaccination (young and adult animals including males) should be added, towards more rapid control results. For the years to follow, lambs and kids kept for restocking (i.e., at 3-4 months of age), could be the only ones to be vaccinated. However, under high prevalence and extensive rearing, such strategy needs regular veterinary supervision and assistance which is very difficult or even impossible to be available everywhere.
- Herd/flock immunity remains more solid when vaccination is associated with the elimination of infected animals. However, such a strategy presupposes effective veterinary services contribution and regular laboratory support.
- For S19 (cattle), vaccine-induced abortions are reduced when the ocular route is adopted. This is not the case for Rev.1 in small ruminants, a well-known abortifacient vaccine. However, in both cases the ocular route reduces the post-vaccine serological response. Thus, although the ocular route is of choice for mass vaccination, the mid-pregnancy period should always be avoided. The late calving/lambing/kidding and lactation seasons are to be selected when mass adult vaccination is performed. However, despite its reduced frequency when vaccination is applied by ocular route, the vaccine strain excretion in the milk has to be considered. Concerning safety in males/bulls, while vaccination with Rev1 is safe, subcutaneous vaccination with S19 is not recommended and its safety given by ocular route is still unknown.
- Another kind of mass vaccination strategy is based on alternate years of vaccination, and is only recommended for extensive animal rearing and poor socio-economic conditions. It can be evaluated for adoption in accordance with countries or zones breeding conditions, epidemiological statistics, level of difficulties for authorities, and breeders' collaboration, among other factors [37-38, 43,45].

Additional control strategies

- The test-and-slaughter strategy, which might gradually lead towards the elimination of infections and establishment of modern cattle farms, cannot be

generally sanctioned for adoption in the SMMER. This is due to a vague epidemiological picture, the need for proficient laboratories, compulsory slaughtering of infected animals, and the lack of adequate funding.

- Expansion of milk pasteurization should become a social and economic strategic target, encouraged by governments-private sectors partnerships and industrial incentives.
- Recruiting different means of mass media for running persistent, extensive and structured public health education campaigns addressing for instance, milk boiling and avoidance of raw milk or fresh white cheese consumption. Such campaigns targeting different population groups including animal breeders, abattoirs workers, housewives, and school children are also helpful in the control of brucellosis.
- It is evident that the level of success of a brucellosis control strategy among animals depends on the best possible consideration of different interconnecting factors and prerequisites fulfilment. The final targets to be reached are the preservation of public health and alleviation of social and economic burdens.

Implementing control plans

Successful implementation of control plans, programs and campaigns necessitates appropriate preparedness plans and organization mechanisms. Of paramount importance is the intersectoral collaboration and coordination within and among animal and public health sectors, as well as seeking the collaboration with the FAO. The integral parts for a proper implementation of such plans, can be summarized as follows:

- Public health and animal health sectors should be empowered with sufficient technical and financial resources as well as an appropriate legal background.
- Animal health personnel should be well trained on the cold chain maintenance and safe use of vaccines.
- Vaccines should originate from the same source, and accepted following quality certification of the seed batch strain, including genetic and biochemical characteristics, by an approved international reference laboratory.
- Vaccine batches to be delivered are accepted following control of the accompanying official quality certification of successful control tests performed, describing each one of them and the obtained results. It is reminded that quality control of the Rev1 vaccine strain is critical due to its tendency to dissociate into a useless R form, which decreases its immunogenicity and increases residual virulence.
- Public health and animal health diagnostic labora-

tories should be well-equipped and staffed with trained personnel. The diagnostic capabilities of the laboratory staff should be checked at intervals through inter-laboratory proficiency. The OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals is an international guide for animal health diagnostic laboratories.

- The quality of diagnostic antigens should be always checked and certified every time a new lot is received/used. Their availability should always be ensured. Technical and financial support to the diagnostic laboratories should be a priority.
- Public health and animal health authorities should coordinate among themselves and exchange data, information and feedback reports vertically and horizontally.
- The progress of the brucellosis control program should be evaluated annually and corrective actions should be adopted where appropriate, or alternative strategies may be considered. A credible indicator for its success is associated with reduction of cases among humans, and abortions among correctly vaccinated flocks.
- Integration with other animal health programs facilitates the development of brucellosis control program, considering its long duration and cost.
- Transboundary livestock's movements necessitate international collaboration and commitments to ensure sustainability of efficient brucellosis and other zoonoses control programs.
- Legislation promulgation and/or amendment should be endorsed where appropriate.

There is no doubt that under the present situation of conflicts, population displacements, and disruption of public health and animal health activities in certain countries such as Iraq and Syria, implementation of prevention and control activity of any communicable disease in humans and/or animals, remains compromised until tranquility and peace prevail [21,46-48].

General management practice

To support brucellosis control activities, a general management practice needs to be implemented as a rule whenever practically possible, even in the absence of a vaccination programme. This should include the following terms and aspects [49]:

- Avoid all contacts between infected and *Brucella*-free animals.
- Eliminate all infected animals without delay.
- Remove all abortion materials in a hygienic way as soon as possible and aborting females should be isolated until a serological diagnosis is confirmed.
- Whenever replacing infected animals with *Brucella*-

free ones, the latter should be kept in quarantine for at least one month to assess their infectious status by serological tests. However, if the brucellosis-free animals are to be introduced among high risk or infected flock animals, they should be first vaccinated.

It is evident that the aforementioned measures, despite their importance, are practically unfeasible under extensive/nomadic rearing conditions, particularly in sheep and goats. However, they constitute a valuable supportive approach in modern cattle farms where management has the possibility to comply with more strictly-controlled practices.

Cost-benefit assessment and benefits from the role of international organizations

When planning a control program, it is essential to assess its expected cost-benefits, being financial and/or social. This includes looking into the facilities available and the appropriate time to start its implementation or its expansion. In this context, different factors and aspects should be considered as priorities together with the availability of resources, examples include:

- _ Prevalence and incidence of brucellosis in humans and livestock per country or zone and their socio-economic impact.
- _ Priority of brucellosis in the area in relation to other public health problems.
- _ Number of livestock in the area and trends of animal population whether increasing, decreasing, or stable.
- _ Type of susceptible livestock breeding (nomadic, transhumant, stationary, or mixed).
- _ Socio-economic conditions, traditional behaviors and awareness level of the population in general, especially in high risk groups.
- _ Public health and animal health services efficiency level, including horizontal intercommunication and coordination levels.
- _ The expected increase in the livestock productivity, together with public health and socio-economic development.

For every community or country, determining the costs and the benefits expected from different strategies facilitates selecting the one combining the highest efficiency in association with its feasibility. It is also important to determine from the beginning which costs should be covered by public funds and which should be supported by private ones.

Besides, tracing human brucellosis cases identified in hospitals and private clinics, is an important passive surveillance measure. This is helpful towards estimating the extension of the problem in certain zones of the country. It also allows an indirect assessment of the progress of

animal vaccination programs over the years, and an additional cost/benefit evaluation factor [1,5,8,45,49-54].

The international organizations

International organizations such as FAO, OIE and WHO, support developing countries through technical and other types of assistance to improve and upgrade the efficiency of their zoonotic and FBDs prevention and control programs. Support measures include expertise sharing, training, capacity building, structural operation, intersectoral collaboration and coordination promotion, public health education, and funds mobilization.

However, in order for this assistance to become really effective for long-term programs, there is an imminent need for these countries to upgrade their infrastructure (central and district services, laboratory support, intersectoral collaboration/coordination level, political commitment). In this context, concerned countries should have recourse to international organizations for advice and support. A good example is the recently promoted FAO project entitled "*A stepwise approach for progressive control of brucellosis in animals and humans*".

Major international organizations such as FAO/UN, WHO, OIE, along with different academic and professional bodies, recognize the interdisciplinary collaboration/integration under the "*One Health*" concept, as a unique approach to be promoted worldwide.

The "*Tripartite Concept Note*" issued in April 2010 by FAO, OIE and WHO, stresses on "*sharing responsibilities and coordinating global activities to address health risks at the animal-human-ecosystems interface*" [6-8, 55-61].

SOCIAL AND ECONOMIC BENEFITS FROM BRUCELLOSIS CONTROL

Following the appropriate implementation of an efficient control program, the most relevant anticipated benefits for a country relate to economic and social benefits [5,50,52,54].

Economic benefits

- _ Increase in the farm animal production (meat, milk, wool, birth rate, etc.).
- _ Increase in quantity and quality of animal products.
- _ Increase in the number of working days per year and per person.
- _ Decrease in the diagnosis, hospitalization and therapy costs.
- _ Decrease in the availability of hospital facilities for other health problems.
- _ Improvement of the country image and better rewards to the national economy.

Social benefits

- Promotion of the physical, psychological and social status of the population.
- Operation and quality development of the animal and public health services as well as administration of the primary health care and hygiene practices.
- Expansion of the awareness of health among rural workers, breeders and the general population.
- Decreased abandonment of farming and other relevant activities by people involved or at risk.
- Reduction in other health and socioeconomic problems, such as food contamination by zoonotic pathogens.

CONCLUSIONS

Brucellosis prevention and control could represent a characteristic prototype of the “One Health” concept to be largely adopted, particularly where the elimination of brucellosis remains far fetched especially among SMME countries in which the disease remains endemic. This concept encompasses coordinating efforts not only among public and animal health authorities, but also among private and national agencies in countries and their leaders as well as liaison coordination with international organizations. Thus, accepting and adopting the provided approaches, as prerequisites and measures of horizontal and vertical collaboration, will surely lead to a successful and efficient brucellosis prevention and control program in any country that needs it.

However, under the present deteriorating situation, conflicts, populations displacements, disruption of public and animal health activities and programs in certain countries of the SMMER, the implementation of any particular activity towards preventing and controlling communicable diseases such as brucellosis remains elusive. It is only when peace is realized, that such control activities can be gradually reestablished for the welfare of the countries.

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