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Review Article

Where will Non-Vitamin K Oral Anticoagulants Stand beyond being Standard of Care in Anticoagulation Therapy?

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Abstract

Objective: Atrial fibrillation (AF) is the most common arrhythmia that increases risk of stroke by 4–5 fold. AF prevalence is approximately 1%–3% in the general population and increases with age. Until 2010, the standard of care (SoC) for prophylaxis of ischemic stroke was Vitamin K antagonists. Phase III randomized controlled trials (RCTs) of non-Vitamin K oral anticoagulants (NOACs) showed that NOACs have comparable or lower risk of stroke, systemic embolism, major bleeding, and death with warfarin in populations with nonvalvular AF (NVAF). Since then, results of these pivotal RCTs were confirmed by postmarketing studies and real-world data. In the last 8 years, they have been replacing warfarin as the SoC not only for preventing stroke in NVAF patients but also for patients with deep vein thrombosis, pulmonary embolism, and those who undergo hip or knee surgery. In recent years, there are emerging data on new clinical areas such as coronary and peripheral artery disease. In this article, it is attempted to review what has changed in the last 8–10 years in the management and prevention of stroke associated with NVAF and other thromboembolic situations and to foresee whether NOACs will be SoC and stand beyond being SoC in anticoagulation therapy. **Methods:** IMS data were obtained from IQVIA with a permission letter on request of Dr. Ergene. IQVIA grants permission to use the statements for the specified purpose (NOACs share in the total anticoagulation market and role of NOACs as the SoC in the near future) of peer-review publication by Dr. Ergene. **Conclusion:** NOACs are breakthrough in stroke prevention, and they will prevail eventually. It will take a few years; anticoagulation market will grow in favor of NOACs, and most probably, NOACs will reach over 50% standard unit market share. It is even more exciting to hear about new therapeutic areas and indications for these agents.

Keywords: Atrial fibrillation, oral anticoagulants, randomized controlled trials

Introduction

Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia with a prevalence of 1%–3% in the general population, reaching 15% in elderly population. Therewithal, it also poses a 4–5-fold increased risk of ischemic stroke, which is increased for elderly patients and a 2-fold increased risk of all-cause mortality.[1-4] On the other hand, AF is a disease with a high economic burden for both patients and healthcare providers.[5] Because of these catastrophic consequences of AF, anticoagulation therapy is indispensable and the standard of care (SoC) for these patients for many years with Vitamin K antagonists (VKA) although some major drawbacks such as bleeding.[6] Non-Vitamin K antagonists (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban have come a long way to become standard therapy. Since 2010, all 4 NOACs have proven their efficacy and safety profile for the prevention of stroke in patients with nonvalvular AF (NVAF). The first evidences in terms of efficacy and safety were obtained with their phase III dose-adjusted, warfarin-controlled, randomized-controlled trials (RCTs). These pivotal trials demonstrated that similar or improved efficacy of NOACs compared with warfarin, in addition to reduced rates of intracranial and life-threatening bleeding.[7-10] A meta-analysis published in 2014 showed that all NOACs had a favorable risk–benefit profile with a significant reduction in stroke,

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intracranial hemorrhage, and all-cause mortality, and with similar major bleeding as for warfarin.[11] In the last 5 years, various and numerous real-world data confirmed these phase III clinical trial outcomes, especially in terms of combined endpoint of intracranial hemorrhage or ischemic stroke.[12-14]

Recent trials which have been conducted in the last couple of years promise wider use of NOACs in new therapeutic areas. One of these new areas is about the use of NOACs in patients with NVAF receiving antiplatelet therapy after percutaneous coronary intervention (PCI).[15-17] Another area is uninterrupted anticoagulation during AF ablation. NOACs became an alternative to VKAs in these procedures.[18,19] In the pathogenesis of acute coronary syndromes (ACSs), plaque disruption and factor Xa play a central role in activation of the coagulation cascade. For this purpose, low-dose rivaroxaban added to dual antiplatelet therapy (DAPT) was tested whether it will improve cardiovascular (CV) outcomes in patients with ACS.[20] It revealed better CV outcomes in the cost of slightly increased risk of bleeding. It might be a new therapeutic option in high-risk ACS patients. In an another recently published trial, low-dose rivaroxaban was tested instead of aspirin with P2Y12 inhibitor in ACS patients. It revealed the safety of rivaroxaban in this setting.[21] In patients with chronic ischemic heart disease, proved antithrombotic strategy is antiplatelet therapy mainly with aspirin. A multicenter trial was conducted whether rivaroxaban alone or in combination with aspirin is more effective than aspirin alone to prevent the recurrence of CV events in patients with stable atherosclerotic disease.[22] This study results with a paradigm shift to anticoagulant therapy in these patient population. Another new therapeutic area is venous thromboembolic disease. In the initial phase of the treatment only rivaroxaban 15 mg bid and apixaban 10 mg bid strategies which approved by regulatory authorities are alternative to VKAs.[23-25] All of the four NOACs approved for remainder of treatment phase. Furthermore, a recently published trial showed benefits of rivaroxaban in extended therapy in chronic phase of venous thromboembolism instead of aspirin.[26]

In summary, in the last 10 years, the development and widespread use of NOACs lead an abundant change and paradigm shift in many therapeutic and preventive areas of CV diseases. Hereafter, it seems that this conversion will expand in other therapeutic areas.

In this article, we tried to review what has changed in the last decade in the management and prevention of stroke associated with NVAF. We also reviewed the evidences which issued NOAC use in other thromboembolic and CV diseases to foresee whether NOACs will be SoC and stand beyond being SoC in anticoagulation therapy.

Methods

IMS data were obtained from IQVIA with a permission letter on request of Dr. Ergene. IQVIA grants permission to use the statements for the specified purpose (NOACs share in the total anticoagulant market and role of NOACs as the SoC in the near future) of peer-review publication by Dr. Ergene. The data are used in accordance with applicable laws and Turkish regulatory authority (Turkish Medicines and Medical Devices Agency).

Results

IMS data of global anticoagulant market showed that trend for either the decrease in VKAs market share or the increase in NOACs market share is continuing in the period from 2014 to 2017 as VKAs decreased from 71.3% to 51.5%; on the contrary, NOACs increased from 16% to 35.7% from 2014 to 2017 [Figure 1].

Discussion

The use of warfarin tends to decrease in the last years due to an increase in NOAC use for several reasons. Time in therapeutic range (TTR) adjustment for warfarin-treated patients is difficult and unpredictable because of its narrow therapeutic window, wide variability in anticoagulant effect, and food/drug interactions.[27-31] TTR data obtained from the real world are much lower than retrieved from randomized controlled trials.[32] The clinical practice guidelines extend the criteria for antithrombotic use and currently recommend NOACs over warfarin.[33]

AF is the most frequent reason for using oral anticoagulant, whereas ACSs (either ST- or non-ST-elevation myocardial infarction or unstable angina) are the leading indication for PCI with stent implantation. Among ACS patients undergoing PCI, approximately 5%–21% of patients have concomitant AF.[15] DAPT plus OAC treatment (triple therapy) that has been used in these patients as a standard treatment has a higher incidence of major bleeding than single antiplatelet plus oral anticoagulant therapy which was shown in WOEST trial.[34] Therefore, one of the trial arm was planned as P2Y12 plus rivaroxaban 15 mg combination without aspirin therapy in phase III PIONEER AF-PCI trial. PIONEER AF-PCI is the first prospective

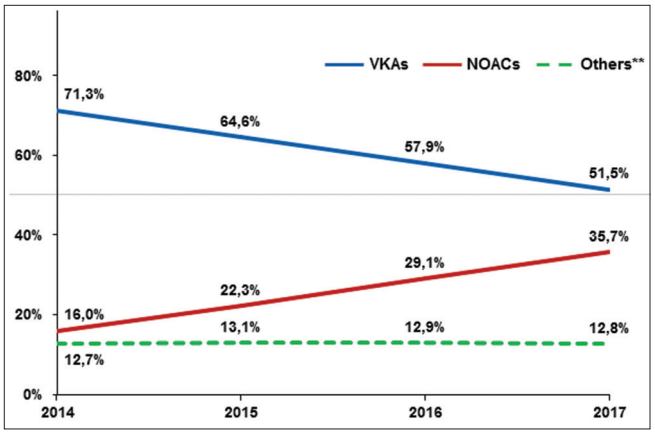


Figure 1: Global AC market volume shares in % (based on DoT*). Source: IQVIA MIDAS, Database: Current All 2017. *DoT = days of therapy, calculated based on volume in SU (standard units). DoT = SU (1 tablet per day) except for dabigatran and apixaban: DoT = SU divided by 2 (two tablets per day) (Adopted with permission from IQVIA Database)

study which evaluated two rivaroxaban dosing regimens. In addition to the above-mentioned dosing regimen, rivaroxaban 2.5 mg twice daily (BID) plus DAPT compared with VKA in patients with NVAF receiving concomitant antiplatelet therapy after PCI, to assess the relative risks of bleeding complications.[15] Rivaroxaban is the first NOAC (versus VKA) which demonstrated significantly improved safety in this patient population. The reduced dose of rivaroxaban 15 mg OD plus single antiplatelet therapy could become a treatment option in this clinical scenario.[15] Other NOACs also have interest in this therapeutic area. In the RE-DUAL PCI study which was recently announced, the safety of dabigatran 110 and 150 mg were compared with warfarin. Both dosing regimens showed significantly lower rates of major bleeding.[16]

In patients with ACS, DAPT is used as standard therapy. Despite this treatment regimen, it is known that there is a residual CV risk.[20] A residual CV risk may be due to the persistence of activation of the coagulation system and significant thrombin formation for several months after clinical stabilization. This may be explaining the rationale for the use of anticoagulant therapy to further reduce recurrent events.[20] Although the benefits of adding warfarin to treatment have been shown in some studies during the last two decades, warfarin has not found a place in this therapeutic area due to the concern of increased bleeding.[28,29,31,32] Recently, two different low doses of rivaroxaban in addition to DAPT were tested for CV outcomes and safety in ATLAS ACS 2-TIMI 51.[20] Rivaroxaban showed a significant reduction in the primary efficacy endpoints of death from CV causes, myocardial infarction, or stroke in patients with a recent ACS and 2.5 mg dose also showed a survival benefit. Regarding safety, there was a nonsignificant slight increase in bleeding with 5 mg dose of rivaroxaban. Conversely, APPRAISE-2 trial which has evaluated apixaban, was prematurely terminated due to an excessive risk of intracranial hemorrhage and major bleeding with triple antithrombotic therapy without a benefit in the risk of recurrent ischemic events.[35] Hereafter, the so-called "vascular dose" is proposed for the low dose of rivaroxaban in patients with ACS. ATLAS ACS-2 TIMI 51 findings demonstrate that increased thrombin activity may play a role in ACS and that NOACs such as rivaroxaban may be a useful option in this treatment regimen.[20] On the other hand, aspirin which has shown benefit in terms of its antiplatelet effect inhibits only the thromboxane A2-dependent pathway of platelet.[36] Since aspirin has a limited antiplatelet effect, a factor Xa inhibitor instead of aspirin was tested in GEMINI study.[21] In this study, it was aimed to assess the safety of using a low dose of the oral anticoagulant rivaroxaban instead of aspirin in patients treated with a P2Y12 inhibitor (either clopidogrel or ticagrelor) in patients with ACS. The similar risk of TIMI non-CABG clinically significant bleeding with rivaroxaban versus aspirin was observed. In summary, low-dose rivaroxaban had similar risk of clinically significant bleeding as aspirin in patients with ACSs.[21]

At the beginning of the last decade, it was determined that DAPT was more effective yet with more bleeding events compared to single acetylsalicylic acid therapy in CURE study.[36] On the other hand, the combination of warfarin and aspirin has shown improved efficacy profile with an increased bleeding rate. Subsequently, ATLAS ACS-2 TIMI 51 study showed improved CV outcomes with an acceptable safety profile with rivaroxaban 2.5 mg bid plus DAPT. The results of this study inspired COMPASS trial; it was conducted whether rivaroxaban alone or in combination with aspirin is more effective than aspirin alone to prevent the recurrence of CV events in patients with stable atherosclerotic disease. One of the most important features of this study was that it was the most comprehensive phase III study conducted in almost 27000 patients who have coronary artery and/or peripheral artery disease, and the study was terminated early due to the overwhelming efficacy since it has met its primary endpoint significantly ahead of time. According to the results of this study, although the rate of major bleeding was higher with the combination of rivaroxaban 2.5 mg bid plus ASA than with aspirin alone as expected, a composite of CV death, stroke, or myocardial infarction was found lower. As a result, the net clinical benefit outcome was better.[22]

Recent retrospective cohort study of Medicare beneficiaries sought to determine patterns of apixaban use and its associated outcomes in dialysis-dependent patients with end-stage renal disease (ESRD) and AF. The study showed that among patients with ESRD and AF on dialysis, apixaban use may be associated with a lower risk of major bleeding compared with warfarin, with a standard 5 mg twice a day dose also associated with reductions in thromboembolic and mortality risk.[37] Recent ACC/AHA focused update paper issued apixaban and warfarin treatment in patients with ESRD with IIb recommendation level. However, its important to recognize that this study has only hypothesis generating not confirming fashion.[38]

VKA has been the standard therapy for patients with a mechanical prosthetic valve, or bioprosthesis with AF. The Dabigatran versus Warfarin in Patients with Mechanical Heart Valves (RE-ALIGN) trial comparing dabigatran etexilate to warfarin was the only randomized controlled study in patients with mechanical valve prosthesis, but it was terminated prematurely because of an excess of thromboembolic and bleeding events among patients in the dabigatran group.[39] To date, use of NOACs is contraindicated for AF patients with mechanical prosthetic valves. The hypothesis of eligibility of use of factor Xa inhibitors in mechanical heart valves was discussed in a recent published paper.[40] The authors emphasize that 1 single trial with a single NOAC does not represent sufficient evidence for dismissing a therapeutic strategy, anticoagulation with NOACs and further experimentation should be conducted in this important area.

In the light of this overwhelming data related to NOACs that we tried to summarize, there are 3 basic questions that must be answered.

Can the NOACs be used in all indications for which warfarin is indicated? Starting from the release of the new agents in

the market, how has the dynamics changed for the global anticoagulant market? What is the future of NOACs in new indications and new therapeutic areas?

The answer of the first question is almost yes. According to clinical practice guidelines, other than severe mitral stenosis and prosthetic valves, NOACs can be used nearly in all indications that VKAs are indicated. In patients with NVAF when oral anticoagulation is indicated, clinical practice guidelines recommend NOACs in preference to a VKA.

The answer of the second question is more complicated and more related to the subject of this article. The answer is not straight forward due to confounding factors such as cost effectiveness and VKAs familiarity of healthcare providers. To what extent are the physicians aware of the benefits of NOACs over VKAs and how much do they adapt to these advantages. On the other hand, healthcare providers have some hesitation in their practice of anticoagulation with VKAs, mostly because of the concerns about bleeding.

The United States (US) health statistics showed that from 2001 to 2011, the relative rate of stroke death decreased by 35%.[41] At that time, this decline was achieved by risk factor management such as controls of hypertension, diabetes, high cholesterol, and smoking cessation. However, the big step was AF management mostly by anticoagulation with VKAs. As NOACs were approved by European and US regulatory agencies in 2008, a contribution of NOAC use to this decline in stroke rate should not be negligible. Although some meta-analysis showed a 19% reduction in stroke and systemic embolism and significantly reduced all-cause mortality with NOACs compared to VKAs, there are no real-world data concerning this issue.[11] Regarding to IMS, data of global anticoagulant market warfarin have declined from 87.5% to 72% through 2008–2014. In the same period, NOACs have reached 15.5% market share [Figure 2]. IMS data also show that same trend for either the decrease in VKAs market share or the increase in NOACs market share is continuing in the period from 2014 to 2017 as VKAs decreased from 71.3% to 51.5%; on the contrary, NOACs increased from 16% to 35.7% from 2014 to 2017. According to 2018 IQVIA Database, 50 million patients have been prescribed rivaroxaban since marketing launch.[42] These data reveal that in the near future, NOACs will be the SoC in anticoagulation therapy.

The third question, what is the future of NOACs in new indications and new therapeutic areas? It is hard to answer this question also, at least now. There are substantial data about factor Xa inhibitor usage in acute and chronic ischemic atherosclerotic heart and peripheral arterial disease albeit only with rivaroxaban. Nevertheless, it is quite early to decide whether in these new therapeutic areas, we should use factor Xa inhibitor, namely rivaroxaban. However, the 2018 European Heart Rhythm Association practical guide recommend low-dose (2.5 mg bid) rivaroxaban in patients with ACS and for secondary prevention of atherothrombotic events in stable CAD in addition to aspirin.[33] Consequently, U.S. Food and Drug Administration,

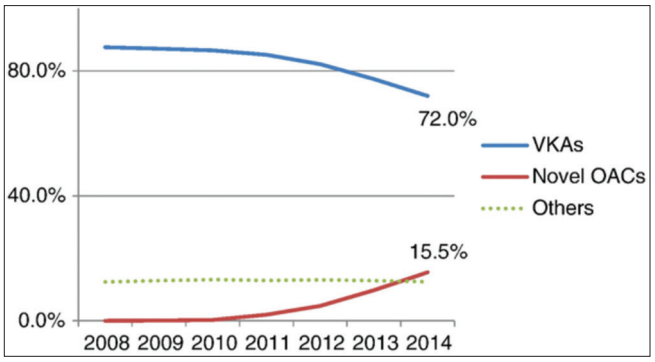


Figure 2: Global AC market volume shares in % (based on DoT*). Source: IMS MIDAS, Database: Current All 2014. *DoT = days of therapy, calculated based on volume in SU (standard Units) (Adopted with permission from IQVIA Database)

European Medicine Agency and Turkish Medicines and Medical Devices Agency (TITCK) have approved rivaroxaban to reduce the risk of major CV events, such as CV death, myocardial infarction and stroke, in people with chronic coronary, or peripheral artery disease. In the near future, medical society will continue discussing the controversial term "vascular dose" of rivaroxaban. We do not know whether there are "vascular doses" of other NOACs. Somehow, it is clear that there is a need for more randomized trials in this new therapeutic areas and new indications for anticoagulant drugs.

Conclusion

As the time pass by, numerous articles regarding the real-world data about NOACs appear on the medical literature. In general, the efficacy and safety of NOACs are confirmed by these real-world data. These drugs are breakthrough in stroke prevention, and they will prevail eventually. It will take a few years; anticoagulation market will grow in favor of NOACs, and most probably, NOACs will reach over 50% standard unit market share. It is even more exciting to hear about new therapeutic areas and indications for these agents.

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Conflicts of interest

The author has made a speech in the field of NOACs for Bayer, Daiichi Sankyo, Pfizer, and Boehringer Ingelheim. The author declares full independence from this funding as to the content of this article.

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Original Article

The Pattern of Reciprocal Electrocardiography Changes in ST-Segment Elevation Myocardial Infarction Patients Presenting with Single-Vessel Disease versus Multi-Vessel Disease

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Abstract

Introduction: The reciprocal ST-segment depression in the electrocardiography (ECG) leads overlying noninfarcting areas was studied previously in acute myocardial ischemia. Multi-vessel disease (MVD) subset of patients have more vague and confusing presentations on ECG; they usually show less ST-segment elevation and profound and diffuse ST-segment depression compared to ST-segment elevation myocardial infarction (STEMI) patients with single-vessel disease (SVD) involving occlusion of one coronary artery only, namely the infarct-related artery (IRA). **Aim of the Work:** The aim was to study and compare the pattern of reciprocal ECG changes in STEMI patients presenting with SVD versus MVD. **Methods and Results:** A total of 125 consecutive patients admitted from April 2014 to August 2015 from the emergency room with the diagnosis of acute STEMI and treated by primary percutaneous coronary intervention (PPCI) at our cath lab at Ainshams University Hospitals (a 24/7 tertiary referral center for PPCI) were included. ST-segment deviations were measured at the J-point. Reciprocal ST-segment changes were identified as per guidelines published by the European Society of Cardiology and the American College of Cardiology, i.e., ST-segment depression ≥0.1 mV in any ECG lead other than aVR, while the cutoff value is different for leads V2 and V3 being only 0.05 mV. Coronary angiographies were evaluated by two independent operators blinded to the clinical and electrocardiographic data. Regarding the left anterior descending (LAD) occlusion, the reciprocal ST-segment depression magnitudes in lead III and in lead arteriovenous fistula (aVF) were significantly less in the MVD group compared to the SVD group, i.e., lead III (−0.08 ± 0.10 mV vs. −0.19 ± 0.15, $P = 0.015$) and lead aVF (−0.07 ± 0.06 mV vs. −0.15 ± 0.11, $P = 0.02$); while regarding the left circumflex coronary artery (LCX) occlusion, the reciprocal ST-segment depression extended significantly in V4 chest lead in the MVD group compared to the SVD group (−0.16 ± 0.08 mV vs. −0.1 ± 0.04, $P = 0.025$); and finally regarding the right coronary artery (RCA) occlusion, the reciprocal ST-segment depression extended significantly in V3 chest lead in the MVD group compared to the SVD group (−0.18 ± 0.07 mV vs. −0.1 ± 0.06, $P = 0.02$). **Conclusion:** The pattern of reciprocal ST-segment depression was more profound when the LAD was the culprit artery causing the anterior STEMI compared to the same case if the LAD was a part of MVD; this does not apply to the LCX and RCA when they were the culprit in cases of inferior STEMI where the MVD group showed more reciprocal ST-segment depression.

Keywords: Reciprocal, ST segment, ST-segment elevation myocardial infarction

Introduction

Electrocardiography (ECG) is the main tool for the diagnosis of ST-segment elevation myocardial infarction (STEMI) and should be performed quickly within 10 min from the first medical contact with a patient presenting with symptoms including typical chest pain suggestive of acute myocardial ischemia. The ECG criteria for the diagnosis of STEMI in the Fourth Universal Definition of Myocardial Infarction include new ST-elevation measured from the J-point in two contiguous leads. The cut-points are ≥1 mm in all leads other than leads

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V2–V3. In V2 and V3, the cut-points are ≥2 mm in males aged 40 years and older; ≥2.5 mm in males younger than 40 years; or ≥1.5 mm in females regardless of age.[1]

The pathophysiology of the elevation of the ST segment in STEMI is due to the current of injury flowing between ischemic and normally perfused myocardial regions.[2] These currents flow during the resting phase and also flow during the phase II of the action potential of the myocardial cells, and they give rise to TQ-segment depression and the true ST-segment elevation in direct-current electrical recordings.[3] The conventional 12-lead ECG machines use alternating current instead of direct current; the TQ- and ST-segment shifts are summed up to be recorded as an overall ST-segment elevation in the 12-lead surface ECG.[4]

The mechanism of reciprocal depression in the ST segment is influenced by multiple factors. First of all, an electrical mirror projection of the ST-segment elevation at a distance from the infarcted area,[5] and secondly, genuine ST-segment depression due to additional subendocardial ischemia at a distance from the infarction due to reduction of the coronary blood flow.[6]

Multi-vessel disease (MVD) subset of patients have more vague presentation on ECG, and sometimes, their ECG findings are confusing; they usually show less ST-segment elevation and profound and diffuse ST-segment depression compared to STEMI patients with single-vessel disease (SVD), involving occlusion of one coronary artery only, namely the infarct-related artery (IRA). Patients with STEMI and MVD may develop superadded subendocardial ischemia at a distance from the infarction. This could magnify the reciprocal ST-segment changes and also counteract the ST-segment elevation in the opposite infarcted region.

Methods

We performed a prospective, single-center, observational study at Ainshams University Hospitals, a tertiary referral hospital with a 24/7 primary percutaneous coronary intervention (PCI) service offered to all incoming STEMI patients. A total of 125 consecutive patients admitted from April 2014 to August 2015 from the emergency room (ER) with the diagnosis of acute STEMI were included. The ECG diagnosis of STEMI was based on the Fourth Universal Definition of Myocardial Infarction and the European Society of Cardiology (ESC) guidelines for STEMI diagnosis,[7] including clinical symptoms suggestive of myocardial ischemia, and the ECG criteria for diagnosis of STEMI in the Fourth Universal Definition of Myocardial Infarction including new ST-elevation measured from the J-point in two contiguous leads. The cut-points are ≥1 mm in all leads other than leads V2–V3. In V2 and V3, the cut-points are ≥2 mm in males aged 40 years and older; ≥2.5 mm in males younger than 40 years; or ≥1.5 mm in females regardless of age. Patients with ECGs that showed changes in the ST-segment secondary to bundle branch block or artificial ventricular paced rhythm were excluded, and patients with normal coronaries or those with nonsignificant lesions upon angiography were also excluded from the study.

The first 12-lead ECG was recorded within 10 min of the first medical contact and recorded as the admission ECG as per guideline recommendations.[7]

ST-segment deviations were measured at the J-point. Reciprocal ST-segment changes were identified as per guidelines published by the ESC and the American College of Cardiology, i.e., ST-segment depression ≥0.1 mV in any ECG lead other than aVR, while the cutoff value is different for leads V2 and V3 being only 0.05 mV. Two cardiologists unaware of the angiographic data revised the electrocardiographic parameters.

Primary PCI (PPCI) was performed in all patients within the first 60 min of presentation to our ER as per the guidelines of revascularization of STEMI patients presenting to PPCI-capable center.[7] The coronary angiograms were revised by two independent operators blinded to the ECG data. The IRA was agreed upon to be identified on the coronary angiogram as the major epicardial coronary artery showing signs of fresh total occlusion or by angiographic evidence of an intraluminal thrombus as seen in the diagnostic coronary injections prior to PPCI. Flow through the culprit artery was graded by using the thrombolysis in myocardial infarction (TIMI) criteria for grading coronary blood flow:[8] TIMI I flow: the epicardial coronary artery shows dye penetration without perfusion. The dye passes beyond the area of obstruction, but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine-angiographic filming sequence; TIMI II flow: partial epicardial coronary perfusion. The epicardial coronary artery shows dye passage across the obstruction and opacifies the coronary artery beyond the obstruction, provided that the rate of entry of dye into the coronaries distal to the obstruction and/or its rate of clearance is slower than its flow into or clearance from other areas that are not perfused by the occluded vessel; and TIMI III flow: the epicardial coronary artery shows complete perfusion. The antegrade flow into the coronary bed beyond the obstruction happens at the same pace as the antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the affected coronary territory is within the same pace as clearance from an unaffected or normal territory.

Any additional coronary stenosis of >70% as visually assessed by two experienced operators blinded to the clinical and ECG data was considered significant.[7] Patients were divided according to the major epicardial coronary IRA into left anterior descending (LAD) group, right coronary artery (RCA) group, and left circumflex coronary artery (LCX) group. In each vessel, we divided the proximal and mid-distal locations of the occlusion taking the first diagonal branch as a reference in the LAD group, the first obtuse marginal branch in the LCX group, and the halfway distance to the acute margin of the heart in cases of the RCA.

The study protocol was approved by the local hospital's medical ethics committee. The Ethical Committee of Ainshams University Hospitals approved the protocol of the study without

further modifications as the study does not involve administration of any new medication under trial or performing an additional procedure rather than the standard PPCI, which is the regular service offered as per the guidelines of clinical practice.

Patients undergoing PPCI procedure which is offered free of charge for all STEMI comers at our center were demanded to sign a consent of approval to the procedure itself including usage of their clinical data in the studies ongoing within our center so long as secrecy and discretion are guaranteed. All data were summarized and displayed as mean ± standard deviation for continuous variables and as number (percentage) of patients in each group for categorical variables. The *P* values for the categorical variables were calculated with the Chi-square test. Continuous variables were compared using the independent sample *t*-test. A two-tailed $P < 0.05$ was considered statistically significant for all analyses. All analyses were performed with the SPSS software (SPSS Inc., Chicago, Illinois, USA).

Results

The demographic and clinical characteristics of the 125 patients presenting clinically and by ECG diagnosis as acute STEMI are listed in Table 1.

Coronary angiography evidenced SVD in 61 patients (48%), two-vessel disease in 32 patients (26%), and three-vessel disease in 32 patients (26%). The percentage of patients with multi-vessel coronary artery disease (CAD) was homogeneously distributed among the three study groups [Table 2].

Regarding the anterior STEMI patients due to acute LAD occlusion, the magnitude of ST-segment elevation was expressed in millivolts, and the distribution of the ST-segment elevation within the ECG leads caused by acute occlusion of the proximal or mid-distal LAD segments was comparable in patients with SVD or MVD, showing a pattern of ST-segment elevation in leads I, aVL, V1 → V6 in the proximal LAD subgroup; ST-segment elevation in V1 → V4 in the mid-distal LAD subgroup; and reciprocal ST depression in leads II, III, and arteriovenous fistula (aVF); however the reciprocal ST-segment depression in leads III and aVF was significantly less in the MVD group compared to the SVD group, i.e., lead III (−0.08 ± 0.10 mV, interquartile range [IQR] [−0.04 to −0.12] vs. −0.19 ± 0.15, IQR [−0.08 to −0.26], $P = 0.015$) and aVF (−0.07 ± 0.06 mV, IQR [−0.01 to −0.13], vs. −0.15 ± 0.11, IQR [−0.1 to −0.21], $P = 0.02$) [Figure 1].

Regarding the inferior/inferolateral STEMI patients due to acute LCX occlusion, there were no isolated posterior MI patients in this study; the magnitude of ST-segment elevation was expressed in millivolts, and the distribution of the ST-segment elevation within the ECG leads caused by acute occlusion of the proximal or mid-distal LCX segments was comparable in patients with SVD or MVD, showing a pattern of ST-segment elevation in leads II, III, and aVF and a comparable pattern of reciprocal ST depression in V2 and V3, but the reciprocal ST-segment depression extended

Table 1: Demographics and clinical characteristics of the study groups

Variable	Major epicardial coronary artery affected, *n* (%)					
	LAD (65 patients)		LCX (14 patients)		RCA (46 patients)	
	Proximal (*n*=41)	Mid and distal (*n*=24)	Proximal (*n*=9)	Mid and distal (*n*=5)	Proximal (*n*=31)	Mid and distal (*n*=15)
Age	59±15	62±13	61±15	58±15	61±14	59±13
Gender (male)	29 (71)	15 (63)	7 (78)	2 (40)	19 (61)	8 (53)
Smoking	21 (51)	11 (46)	6 (67)	1 (20)	17 (55)	6 (40)
Hypertension	27 (66)	18 (75)	7 (78)	2 (40)	22 (71)	7 (47)
Diabetes mellitus	23 (56)	15 (63)	5 (56)	2 (40)	19 (61)	5 (33)
Dyslipidemia	24 (59)	13 (54)	4 (44)	3 (60)	16 (52)	8 (53)
Positive family history	11 (27)	6 (25)	3 (33)	2 (40)	8 (26)	4 (27)

Data are presented as mean±SD or *n* (%). SD: Standard deviation, LAD: Left anterior descending, LCX: Left circumflex coronary artery, RCA: Right coronary artery

Table 2: Number and distribution of major epicardial coronary arteries affected

Number of major epicardial coronary arteries affected	Major epicardial coronary artery affected					
	LAD (65 patients)		LCX (21 patients)		RCA (39 patients)	
	Proximal (*n*=41)	Mid and distal (*n*=24)	Proximal (*n*=11)	Mid and distal (*n*=10)	Proximal (*n*=25)	Mid and distal (*n*=14)
Single-vessel disease (*n*=61)	25 (61)	11 (46)	5 (45.5)	3 (30)	11 (44)	6 (43)
Two-vessel disease (*n*=32)	9 (22)	8 (33)	1 (9)	3 (30)	7 (28)	4 (28.5)
Three-vessel disease (*n*=32)	7 (17)	5 (21)	5 (45.5)	4 (40)	7 (28)	4 (28.5)

Data are presented as *n* (%). LAD: Left anterior descending, LCX: Left circumflex coronary artery, RCA: Right coronary artery

significantly in V4 chest lead in the MVD group compared to the SVD group (−0.16 ± 0.08 mV, IQR [−0.12 to −0.19], vs. −0.1 ± 0.04, IQR [−0.08 to −0.12], $P = 0.025$) [Figure 2].

Regarding the inferior/inferolateral STEMI patients due to acute RCA occlusion, the magnitude of ST-segment elevation was expressed in millivolts, and the distribution of the ST-segment elevation within the ECG leads caused by acute occlusion of the proximal or mid-distal RCA segments was comparable in patients with SVD or MVD, showing a pattern of ST-segment elevation in leads II, III, and aVF and a comparable pattern of reciprocal ST depression in leads I, aVL, and V2, but the reciprocal ST-segment depression extended significantly in V3 chest lead in the MVD group compared to the SVD group (−0.18 ± 0.07 mV, IQR [−0.15 to −0.21], vs. −0.1 ± 0.06, IQR [−0.08 to −0.12], $P = 0.02$) [Figure 3].

Discussion

The reciprocal ST-segment depression seen in the ECG leads recording electrical activity from noninfarcting regions has been reported in previous studies on acute myocardial ischemia.[9,10] The mechanism is complex with multiple interplaying factors.[11,12]

MVD subset of patients have more vague presentation on ECG, and sometimes, their ECG findings are confusing; they usually show less ST-segment elevation and profound and diffuse ST-segment depression compared to STEMI patients with SVD involving occlusion of one coronary artery only,

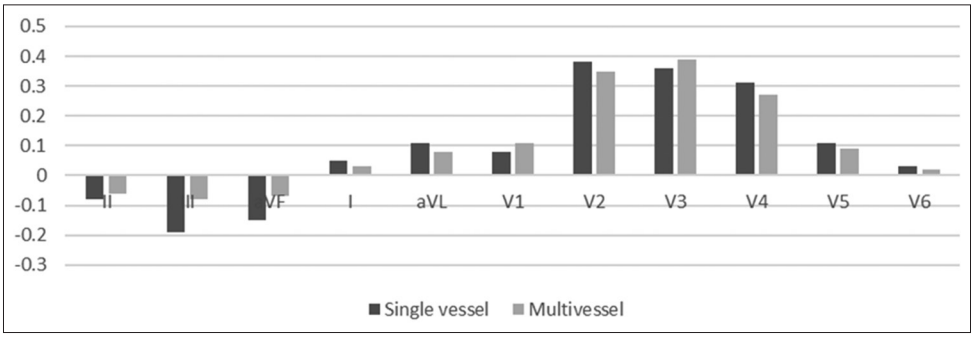


Figure 1: Pattern of ST-segment deviation in the electrocardiography leads in patients presenting with acute left anterior descending occlusion. Values represent the mean ST-segment deviations in millivolts

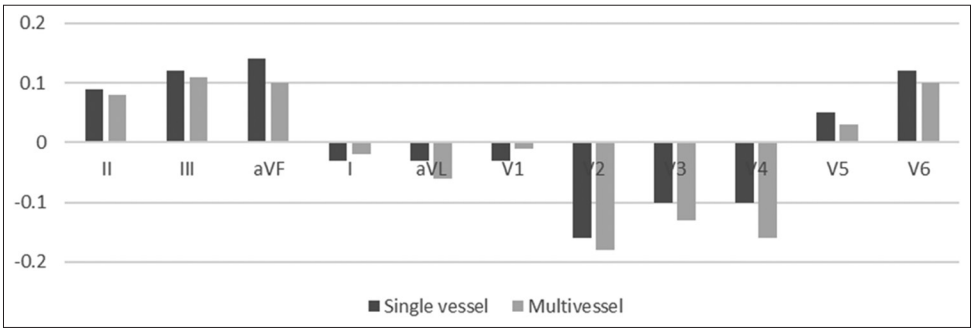


Figure 2: Pattern of ST-segment deviation in the electrocardiography leads in patients presenting with acute left circumflex coronary artery occlusion. Values represent the mean ST-segment deviations in millivolts

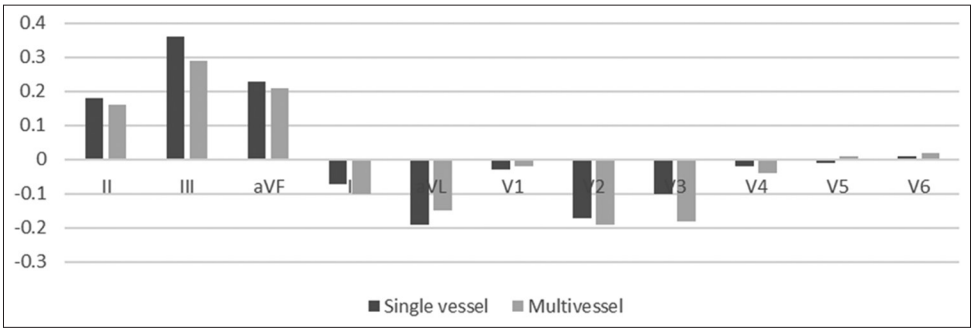


Figure 3: Pattern of ST-segment deviation in the electrocardiography leads in patients presenting with acute right coronary artery occlusion. Values represent the mean ST-segment deviations in millivolts

namely the IRA. Patients with STEMI and multi-vessel CAD involving coronary stenosis approaching the critical 90% level of luminal stenosis may develop superadded subendocardial ischemia at a distance from the infarction, and this could magnify the reciprocal ST-segment changes and counteract the ST-segment elevation in the opposite infarcted region.[13]

The pathological mechanisms include an electrical mirror projection of the ST-segment elevation observed in the reciprocal (mirroring) leads,[5] and/or in combination with a true ischemic ST-segment depression caused by additional subendocardial ischemia remote from the infarction due to reduction of the coronary blood flow.[6]

Our study showed that, regarding the LAD occlusion, the reciprocal ST-segment depression in leads III and aVF was significantly less in the MVD group compared to the SVD group, while regarding the LCX occlusion, the reciprocal ST-segment depression extended significantly in V4 chest lead in the MVD group compared to the SVD group, and finally regarding the RCA occlusion, the reciprocal ST-segment depression extended significantly in V3 chest lead in the MVD group compared to the SVD group.

The mechanism of electrical mirroring[5] may explain our results regarding LAD being the IRA in the subset of patients presented with anterior STEMI; the SVD group in our study showed more profound reciprocal ST-segment depression compared to the MVD group, this could be explained by the physical fact of mirroring the electrical changes, where the ST-elevation magnitude is directly mirrored as a negative deflection in the reciprocal leads in the SVD group without being affected by another ischemic electrical deflection of the ST segment from another territory. While in the MVD group, transmural ischemia in opposite territories may attenuate the reciprocal ST-segment changes in the anterolateral chest leads,resulting in a lesser amplitude of negative deflections in the inferior leads.[14,15]

The ischemia at a distance explanation[6] can verify the pattern of observed reciprocal ST-segment changes in the LCX and RCA groups of patients in our study; this is explained by the volume and distribution of coronary collateral vessels that reduce the extent of myocardial ischemic burden caused by acute blockage of a major epicardial vessel. In the case of extensive MVD, when those collaterals are fed by the IRA and feeding another critically stenosed major epicardial vessel, the distribution of reciprocal ST depression will be wider and involving more leads with more negative amplitude due to more profound ischemia at a distance once the IRA is totally occluded.

Conclusion and Study Limitations

Data from this study show two major important results; first of all, the pattern of reciprocal ST-segment depression was more profound when the LAD was the IRA causing the anterior STEMI compared to the same case if the LAD was a part of MVD, and the second result is that this does not apply to the LCX and RCA when they were the IRA in cases of inferior STEMI; still the MVD group showed more reciprocal ST-segment depression.

There are several important limitations in this study. This was a single-center, nonrandomized observational study although we included consecutive patients. Future larger studies on bigger samples are required to confirm these preliminary results.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

A Safe and Rapid Technique for Pacemaker İmplantation: Roadmap-Guided Subclavian Vein Puncture

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Abstract

Objective: Widely used method is blinded puncture of subclavian vein, but the complication rate is high in this method. In this study, we aimed to demonstrate the effect of roadmap use during implantation of permanent pacemaker on the success rate, speed of puncture and complications. **Methods:** The study was designed as a prospective randomized controlled study. Totally, 125 devices were implanted to the patients included in the study, and 518 punctures were performed for implantation of these devices. 186 punctures were performed in roadmap group and 332 punctures were performed in conventional group. Two groups were compared with regard to clinical and demographic features, speed and success of puncture and complications. **Results:** Baseline characteristics were similar between groups. Median duration of intervention for each puncture was 27 (15/46) s in roadmap group and 56 (30/100) s in conventional group. The number of attempts for a successful puncture was detected as 1 (1/2) in roadmap group and 2 (2/4) in conventional group. Arterial puncture incidence was 10.3% in roadmap group and 37% in conventional group ($P < 0.001$ for all). Considering complications, the incidence of pneumothorax and intramuscular puncture was seen lower significantly ($P = 0.046$ and $P = 0.006$, respectively). **Conclusion:** Number of attempts for successful puncture, time needed for successful puncture, number of arterial puncture and complication rate was significantly lower in patients undergoing pacemaker implantation by roadmap technique. Based on these data, roadmap technique may take the place of conventional method of puncture.

Keywords: Defibrillator, pacemaker, roadmap, subclavian puncture

Introduction

Subclavian venous access is preferred frequently for implantation of permanent pacemakers since it allows the implantation of multiple leads in a reasonable period.[1,2] Procedural success and complication rate is closely related with the operator experience and the anatomy of the operation area. Blinded punctures performed with conventional method can cause various complications. In the case of failed punctures, repeated attempts increase the risk of complications such as pneumothorax, hemothorax, lung laceration, arteriovenous fistula, and injury to brachial plexus.[3,4] Contrast venography-guided puncture of the subclavian vein has been used to increase the success rate of the procedure and to avoid the complications. In this method, venous anatomy has been visualized by 15–20 cc of contrast agent

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injection made from the ipsilateral peripheral venous access and subclavian puncture has been performed under fluoroscopy.[5,6] Punctures performed between costoclavicular ligament and subclavian muscle can cause lead fractures later on.[7] It is difficult to avoid this complication in punctures achieved by conventional method in which extrathoracic and intrathoracic subclavian vein discrimination cannot be done. Similarly, the complication rate including lead fractures decreased in studies determining extrathoracic subclavian vein anatomy to avoid lead fractures.[8,9] In addition, ultrasonography-guided intervention of axillary vein also reduced lead fractures and other complications related with the subclavian venous puncture.[10]

Roadmap is an imaging technique that is created by converting the first image taken during injection to digital information and holding it in the device memory. It is important to visualize the vascular bed simultaneously that allows the positioning of the guide wires and catheters without need for repetitive contrast injections. The usage of roadmap increases the success rate and speed of the cannulation.[11]

In this study, we aimed to investigate the effect of roadmap use during the implantation of permanent pacemaker on the success rate and speed of venous puncture, and number of attempts for successful puncture as well as to various complications such as arterial puncture, intramuscular puncture, pneumothorax, and pocket hematoma.

Methods

Patient selection

The study was designed as a prospective randomized controlled study. Patients over 18 years old who were taken to catheterization laboratory for permanent pacemaker implantation through the subclavian vein were included in the study. Patients were divided into two groups: those who underwent roadmap-guided subclavian venous puncture and those who performed conventional subclavian venous puncture. Both puncture techniques performed separate puncture for each lead implantation. In both groups, demographic characteristics, the total number of punctures performed, number and type of inserted devices, time for successful punctures, time for single successful intervention, number of arterial punctures, clinical and laboratory data before and after the procedure, and complications after the procedure were recorded. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dl or taking antidiabetic medication. Hypertension was defined as systolic arterial blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg measured on three separate office visit or taking antihypertensive treatment. The pacemaker implantation decision was made by our heart team including electrophysiologists and heart failure experts in accordance with related guidelines of the European Society of Cardiology and pacemaker implantation was performed by the same electrophysiologist in both groups.

Pacemaker implantation procedure

All patients were questioned whether receiving antiaggregant and anticoagulant therapy before the procedure and if necessary, they were managed properly, and the treatments were recorded. The implantation area was cleared off skin hairs 24 h before the procedure. Nasal oxygen was given to the patients when needed. All patients were sedated by intravenous midazolam (1–2.5 mg) to perform a smooth implantation. Flumazenil was kept for use when required. Appropriate antibiotic prophylaxis was given to the patients before the procedure. Two venous vascular accesses were established in all patients. One of them was placed on ipsilateral antecubital region with the proper venous catheter for delivering contrast material to generate a roadmap in the roadmap group.

Following skin preparation and local anesthesia, the skin incision was made 2 cm below and parallel to the clavicle, as the medial edge of incision ending in 1/3 middle part of the clavicle. The length of incision was 4–6 cm for implantable cardioverter defibrillators (ICDs) and 3–4 cm for pacemakers. After progressing toward pectoralis muscle fascia by blunt and sharp dissection, a pocket proper for device size was created under the muscle to decrease the erosion and to get a favorable appearance cosmetically based on the operator's choice. Then, in conventional subclavian venous puncture group, 2–3 ml saline was taken by conventional 18-gauge needle mounted to 10 cc injector and the puncture was performed from the point combining middle and inner third of clavicle by progressing the needle under the clavicle with the needle tip pointing the upper notch of the sternum. The duration of the intervention was defined as the time between the beginning of the puncture and cannulation of the subclavian vein. The repeated intervention was defined as the removal of the needle from the puncture area completely and beginning the puncture from a different region. Arterial puncture was defined as the puncture of the subclavian artery accidentally. An independent observer calculated the duration of each successful venous puncture. Number of attempts for venous cannulation and number of arterial puncture was also recorded. In the roadmap group, after stabilization of the arm, a roadmap was formed by injecting 15 ml of contrast agent through antecubital venous line [Figure 1]. The puncture was performed in the

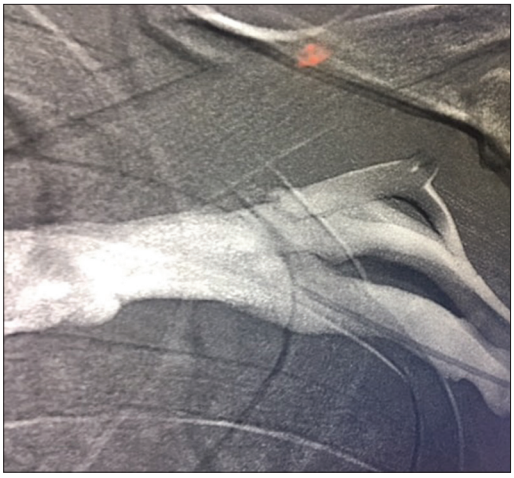


Figure 1: Roadmap-guided subclavian vein puncture

same way as described above and time to puncture, number of attempts for venous cannulation and number of arterial puncture was also recorded. Fluoroscopy duration required for creating roadmap was recorded by an angiography technician. The total fluoroscopy time was also noted if fluoroscopy was needed in the conventional procedure group. After the implantation and fixation of the leads, the pocked irrigated with antibiotic (rifocine) and pacemaker generator was inserted into the pocket enabling that the portion of leads outside the vein are placed under the generator which was fixed by a single suture. Then, the incision was sutured and the pacemaker was programmed. Pressure was applied on to the incision area by 1000 cc physiological saline solution pack for 2 h. Patients were followed up for 24–48 h. Any complication such as pneumothorax and pocket hematoma was recorded. Ten days later, incision area was reevaluated during the removal of the sutures, and any complication such as wound infection was recorded.

This study was approved by the Ethics Committee of the Kahramanmaras Sutcu Imam University under protocol number 52. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Statistical analysis

Statistical analyses were conducted through SPSS 17.0 (for Windows SPSS 17.0, Chicago, Illinois, USA). Continuous variables were presented as mean ± standard deviation (for parameters with normal distribution) and median (25%/75% interquartile range) for parameters without normal distribution, and categorical variables were presented as percentages. Normality analysis was performed using the Kolmogorov–Smirnov test. Comparison of categorical variables between the groups was performed using the Chi-square test. The Student's *t*-test was used for the comparison of normally distributed variables, and the Mann–Whitney U-test was used for the comparison of normally distributed multiple variables. A two-tailed $P < 0.05$ was determined to be statistically significant within a confidence interval of 95%.

Results

Randomization phase

In study, 126 patients were enrolled consecutively and randomized (1:1) either to conventional group or roadmap group. One of the patients who received a single-chamber pacemaker with the roadmap method was excluded from the study because of withdrawing consent. Two patients in the conventional group were switched to roadmap group due to failure of subclavian vein puncture with conventional method. Accordingly, roadmap group composed of 64 patients and conventional group consisted of 61 patients. For a total of 125 devices, 245 leads were implanted. Operators received a deadline of 5 min or 8 subclavian vein puncture to complete the conventional method subclavian vein puncture.

Baseline characteristics of study population are presented in Table 1. Of these patients, 45 (36%) underwent single chamber (SC) ICD/pacemaker, 40 (32%) underwent dual chamber (DC) ICD/pacemaker, and 40 (32%) underwent CRT implantations. Roadmap-guided implantation was performed in 64 patients (22 [35%] SC ICD/pacemaker, 22 [34%] DC ICD/pacemaker, and 20 [31%] CRT) while the implantation was performed by conventional method in 61 patients (23 [37%] SC ICD/pacemaker, 18 [30%] DC ICD/pacemaker, and 20 [33%] CRT). There was no significant difference between groups considering SC ICD/pacemaker, DC ICD/pacemaker, and CRT implantation ratios ($P = 0.881$, $P = 0.645$, and $P = 0.759$, respectively). Demographic data of the patients were given in Table 1. Groups were similar for basal characteristic features. There was no statistically significant difference between groups considering hematological and biochemical parameters [Table 1].

Table 1: Baseline characteristics of study population

Baseline characteristics	All patients ($n=125$)	Roadmap group ($n=64$)	Conventional group ($n=61$)	*P*
Age, years*	67 (58/75)	65 (57/72)	68 (58.5/76)	0.149
Weight, kg	73.4±12.3	72±11.1	74.8±13.7	0.198
Height, cm*	161 (155/168)	158 (154.25/163.75)	164.5 (159.25/170.75)	<0.001
Gender, male/female, *n* (%)	90/35 (72/28)	45/20 (69.2/30.8)	45/15 (75/25)	0.473
Hypertension, *n* (%)	81 (64.8)	41 (63.1)	40 (66.7)	0.761
Diabetes mellitus, *n* (%)	56 (44.8)	29 (44.6)	27 (45)	0.972
Current smoking, *n* (%)	79 (63.2)	42 (64.6)	37 (61.7)	0.647
Hyperlipidemia, *n* (%)	82 (65.6)	46 (70.8)	36 (60)	0.163
COPD, *n* (%)	30 (24)	15 (23.1)	15 (25)	0.839
CAD, *n* (%)	95 (76)	49 (75.4)	46 (76.7)	0.989
SC pace or ICD, *n* (%)	45 (36)	23 (35.4)	22 (36.7)	0.881
DC pace or ICD, *n* (%)	40 (32)	22 (33.8)	18 (30)	0.645
CRT, *n* (%)	40 (32)	20 (30.8)	20 (33.3)	0.759

*Data presented as median (25/75% IQR). CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRT: Cardiac resynchronization therapy, DC: Dual chamber, ICD: Implantable cardioverter defibrillator, SC: Single chamber, IQR: Interquartile range

On the comparison of outcomes, it was seen that 186 punctures were performed in roadmap group and 332 punctures were done in conventional group. The median duration of intervention for each puncture was 27 s (15/46) in roadmap group and 56 s (30/100) in conventional group. The number of attempts for a successful puncture was detected as 1 (1/2) in roadmap group and 2 (2/4) in conventional group. Arterial puncture incidence was 10.3% in roadmap group and 37% in conventional group. Time to puncture, number of attempts for successful puncture and arterial puncture ratio was seen significantly lower in roadmap group ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively). When peri- or post-procedural complications were compared, incidence of pneumothorax and intramuscular puncture was seen lower significantly ($P = 0.046$ and $P = 0.006$, respectively). Although pocket hematoma was seen less frequently in roadmap group, the difference between groups was not statistically significant ($P = 0.075$). The groups were found similar as the success of the procedure ($P = 0.113$) [Table 2].

When mean duration of puncture, number of attempts for successful puncture and ratio of arterial puncture were compared according to device type, it was found that usage of roadmap method for device implantation reduced the time needed for successful puncture, number of attempts for successful puncture and incidence of arterial puncture significantly in all types of devices. In patients undergoing VR and DR pacemaker/ICD implantation, total procedure time was less in road map group whereas in patients performed CRT implantation, total procedure times were same in both groups. Considering fluoroscopy durations, images were taken from all patients by the way of fluoroscopy for 5 s in road map group. Then, puncture was performed and no additional fluoroscopy was performed. In conventional group, fluoroscopy was not performed in successful blinded punctures, but fluoroscopy times required for venography and anatomic localization were recorded. These durations were found as 20 s (0/40) for VR and 20 s (0/43) for DR and were significantly higher as compared to those of road map group ($P = 0.001$ for both). In CRT implantations, fluoroscopy times used for cannulation of coronary sinus were longer and were found similar between two groups (28.3 ± 6.0 vs. 30.7 ± 8, $P = 0.286$) [Table 3].

Table 2: Procedural characteristics and complication frequencies of both groups

	Roadmap group ($n=64$)	Conventional group ($n=61$)	*P*
Total/successful punctures, *n*	186/126	332/119	<0.001
Failed attempts, *n* (%)	60 (32.3)	213 (64.2)	<0.001
Time to puncture, s*	27 (15/46)	56 (30/100)	<0.001
Attempts for successful puncture, *n**	1 (1/2)	2 (2/4)	<0.001
Incidence of arterial puncture, %	10.3	37	<0.001
Incidence of pneumothorax, %	0.8	5	0.046
Incidence of intramuscular punctures, %	0	5.9	0.006
Incidence of pocket hematoma, %	1.6	5.9	0.075

*Data presented as median (25/75% IQR). IQR: Interquartile range

Table 3: Procedural characteristics of both groups according to device types

	Roadmap group ($n=64$)	Conventional group ($n=61$)	*P*
SC ICD/pace, *n*	22	23	-
Attempts for successful puncture, *n**	1 (1/2)	3 (1/4)	0.004
Time to puncture, s*	30 (23/70)	145 (18/180)	0.014
Incidence of arterial puncture, %	9.1	30.4	0.063
Fluoroscopy times, s*	5 (5/5)	20 (0/40)	0.001
Total procedure time, min*	26±5.1	30.6±7.2	0.017
DC ICD/pace, *n*	22	18	-
Attempts for successful puncture, *n**	1 (1/2)	2 (1.25/4)	<0.001
Time to puncture, s*	25 (10/37.25)	63.5 (22.25/86.25)	<0.001
Incidence of arterial puncture, %	9.1	33.3	0.006
Fluoroscopy times, s*	5 (5/5)	20 (0-43)	0.001
Total procedure time, min*	33.7±5.2	39.9±5.9	0.001
CRT, *n*	20	20	-
Attempts for successful puncture, *n**	1 (1/2)	2 (2/4)	<0.001
Time to puncture, s*	26 (15/46)	47 (30/97)	<0.001
Incidence of arterial puncture, %	11.7	40.3	<0.001
Fluoroscopy times, min*	28.3±6.0	30.7±8	0.286
Total procedure time, min*	65 (40/100)	65 (45/120)	0.242

*Data presented as median (25/75% IQR). IQR: Interquartile range, DC: Dual chamber, SC: Single chamber, CRT: Cardiac resynchronization therapy, ICD: Implantable cardioverter defibrillator

Discussion

This is the first study evaluating the effect of roadmap use on the success and the complication rate of the implantation of permanent pacemakers. The study revealed that complication rate was lower; success rate of puncture was higher; fluoroscopy time, total procedure time, and time to puncture were lower in patients undergoing permanent pacemaker implantation using roadmap technique. Since roadmap technique allows the anatomic imagination of subclavian vein, cannulation of extrathoracic portion of subclavian vein may prevent punctures through the muscle and decrease the probability of lead fractures.

Nowadays, the subclavian vein is preferred for permanent pacemaker implantation because of rapid and easy applicability. The number of attempts and time for successful puncture of subclavian vein depends on both anatomical factors and operator experience. A technique that can minimize the unfavorable effect of these two factors is supposed to decrease both the rate of puncture failure and duration of successful puncture. Accordingly, this will reduce the complications related with puncture and increase patient comfort because of less number of trials for successful puncture and shorter procedure duration. Previously, Higano *et al*. and Chan *et al*. performed subclavian puncture by the guidance of fluoroscopic venography in their studies and reported that puncture guided by venography was safer.[6,7] Similar to these studies, we planned to compare subclavian puncture performed after anatomic imagination of subclavian vein with conventional blinded puncture. But differently, we used roadmap technique to visualize subclavian vein. There are several advantages of roadmap technique to venography. One of them is shortened fluoroscopy duration and accordingly decreased exposure of both patient and operator to radiation. The other one is that single roadmap image enables opportunity to multiple attempts of puncture; so recurrent use of contrast agent during the implantation of pacemakers with multiple leads is avoided. However, in the group of patients performed conventional method, there is no need for fluoroscopy and contrast injection during successful venous puncture. In case of contrast agent allergy or renal impairment, blinded puncture is superior to roadmap or fluoroscopy-guided techniques. On the other hand, when the intervention is considered under fluoroscopic venography due to anatomical difficulties or unsuccessful attempts, then the use of roadmap method may be more reasonable unless there is no contraindication to contrast agents.

Although various studies comparing different techniques used for intervention are present in the literature, our study is the first one using roadmap technique for subclavian puncture.[8,9,12,13] In this study, blinded subclavian venous puncture was compared with the puncture guided by roadmap with regard to success of the procedure, time needed for a successful venous puncture and unintended puncture of subclavian artery, and roadmap technique was found superior to blinded puncture in all these parameters. Main complications of subclavian venous puncture are pneumothorax and hemothorax, and their incidence is 1%–3%.[14] In order to decrease these complications venography has been used frequently and shown to be effective in various studies.[6,15,16] In our study, pneumothorax was reported only in the blinded puncture group. Higher number of attempts for successful puncture in this group may be a causative factor for these complications.

Pocket hematoma is a widely seen complication of pacemaker implantation.[17] It increases the duration of hospitalization and the risk of device infection. Many factors may contribute to development of pocket hematoma. Procedure type (first implantation or reimplantation), operator experience, device size, number of leads, venous route (subclavian or cephalic vein), body mass index and anticoagulant and/or antiaggregant use are regarded among them.[18-22] In our study, pocket hematoma was shown to be more frequent in the group of blinded puncture. Detailed analysis revealed that unintended puncture of subclavian artery was performed in most of the patients having pocket hematoma. This finding made us to think that subclavian arterial puncture could be a contributing factor for pocket hematoma. However, further studies are needed to support this hypothesis considering the factors predisposing to pocket hematoma such as device size, number of leads implanted, and patient's medication.

Another problem that can be encountered during subclavian puncture is puncture of intrathoracic subclavian vein that can result in lead fracture. Intrathoracic subclavian puncture causes trapping of leads between costoclavicular ligament and/or subclavian muscles which results in lead fractures.[5] Based on these data, we intended to puncture extrathoracic subclavian vein in the patients of roadmap group. In blinded puncture, since we could not do this discrimination, there were some intramuscular punctures, which were identified by the factors based on the operator experience such as resistance to the insertion of sheath and resistance and difficulty during manipulation of leads after removal of sheath. Puncture site was changed in these patients to decrease the risk of lead fracture. Roadmap-guided puncture may provide to avoid intramuscular puncture and/or intrathoracic puncture of subclavian vein, which is the most important cause of lead fractures, independently of operator experience. As a result, lead fractures can be prevented by this technique.

Study limitations

Our study has some limitations. Of these, number of study population was relatively small and all pacemakers were implanted by electrophysiologists. The roadmap technique has also some limitations such as keeping the patient immobile and use of contrast agents for visualization of the vein. Although we thought that lead fractures might be prevented by puncture of extrathoracic subclavian vein, we could not document the rate of lead fracture since long-term follow-up was not done. Finally, the team conducting the study will also report the results. This is an important limitation for bias.

Conclusion

Our study revealed that number of attempts for venous puncture was lower and time needed for successful puncture was shorter in patients undergoing pacemaker implantation by roadmap technique. Moreover, complications of pacemaker implantation such as pneumothorax, hemothorax, and pocket hematoma were seen less frequently in roadmap group. These data indicate that procedure of pacemaker implantation can be managed more successfully and safely using roadmap technique.

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Conflicts of interest

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Original Article

Evaluation of Cardiac Arrhythmia Incidence in Patients Treated with Oral Moxifloxacin

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Abstract

Background: The effect of moxifloxacin on QT interval is reversible and dose related, mainly provided by weakly but rapidly activated rectifying potassium channel blockade, IKr or human ether-a-go-go-related gene potassium channels. Retrospective data suggested an increase in cardiac event rates with moxifloxacin use. Nevertheless, except for case reports and experimental trials about QT/QTc, there are insufficient data in the literature on the incidence of cardiac arrhythmias detected by electrocardiography (ECG) and Holter monitoring. In this trial, we sought to determine the effects of newly administrated oral moxifloxacin on the incidence of cardiac arrhythmias. **Methods:** Forty-four patients (mean age 34.0 ± 10.4 years) treated with oral moxifloxacin with the indications of upper airway infections, community-acquired pneumonia, and acute exaggerated bronchitis were enrolled. All patients were screened for cardiac arrhythmia before therapy (BT) (0^{th} day), on the 3^{rd} day (during therapy [DT]), and on the 10^{th} day (after therapy [AT]) with ECG and on the 3^{rd} and 10^{th} day with Holter monitorization. Before starting of the therapy, structural heart diseases were excluded using echocardiography, and other exclusion criteria were based on the laboratory tests. **Results:** The mean heart rate (HR) assessed by Holter monitoring was not significantly different during and after antibiotic therapy, although the mean HR measured from surface ECG was significantly reduced during and after antibiotic therapy compared to baseline (BT: 80.3 ± 13.9 beats per minute [BPM] vs. DT: 76.3 ± 11.3 vs. BPM vs. AT: 75.9 ± 106.0 BPM; $P = 0.007$). The mean QT interval value was increased on the 3^{rd} day when compared to 0^{th} day and was similar with the value on the 10^{th} day (BT: 353.1 ± 24.6 msn vs. DT: 363.3 ± 23.7 msn vs. AT: 361.8 ± 20.8 msn; $P = 0.034$). The mean QTc interval was significantly increased on the 3^{rd} day; however, it was decreased to the baseline value AT (BT: 396.4 ± 20.2 msn vs. DT: 404.4 ± 19.3 msn vs. AT: 397.5 ± 21.0 msn; $P = 0.011$). When the Holter monitoring findings of our study were analyzed in terms of gender interaction, minimal and maximal HR and QT dispersion parameters as well as the frequencies of ventricular and supraventricular extrasystoles and other arrhythmia findings were not different between male and females. **Conclusion:** Oral moxifloxacin started on an outpatient basis with the indication of airway infections resulted in a temporary increase in QT interval DT. However, it does not affect QTc and is not related with serious cardiac arrhythmias during Holter monitoring.

Keywords: Arrhythmia, electrocardiography, Holter monitoring, moxifloxacin, QT dispersion, QT/QTc interval

Introduction

Moxifloxacin is a fluoroquinolone used for community-acquired pneumonia, bronchitis exacerbations, and genitourinary diseases but mainly for the treatment of other upper and lower respiratory tract infections.[1,2] The effect of moxifloxacin on QT interval in electrocardiography (ECG) is reversible and dose related, resulted by weakly but rapidly activated

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rectifying potassium channel blockade (IKr)[3] or human ether-a-go-go-related gene (HERG) potassium channels.[4] There are several data reporting an increase in cardiac events related with the usage of oral moxifloxacin.[2,3,5] The common side effects of oral moxifloxacin are well known as gastrointestinal and central nervous system side effects, allergic reactions, skin lesions, tendinitis, QT/QTc prolongation, hypoglycemia, hyperglycemia, and hematologic side effects.[6] QT prolongation is more pronounced with the usage of the certain drugs such as amiodarone. Moxifloxacin should not be used with QT prolonging drugs because of the risk of torsades de pointes (TdP) type of arrhythmia and sudden cardiac death.[7] There is a long list of drugs prolonging QT interval including psychotropic (pimozide, sertindole, ziprasidone, quetiapine, haloperidol, and thioridazine),[8,9] antihistaminic (astemizole and terfenadine), and antimicrobial/antimalarial (erythromycin, cetoconazol, chloroquine, and halofantrine)[3,4] agents. Despite the fact that the risk of TdP with usage of oral moxifloxacin is very low as well as with other fluoroquinolones (<0.01%), it is still suggested to avoid using with other QT/QTc prolonging drugs, especially in high-risk groups.[10] However, except for case reports and experimental trials in the literature, there is not any clinical study evaluating the incidence of cardiac arrhythmias on ECG and Holter monitoring with the usage of oral moxifloxacin.

Methods

This prospective, case–controlled study was conducted at the Department of Cardiology, Faculty of Medicine, Başkent University. In this trial, 44 patients (20 females) between 18 and 75 years of age (mean 34.0 ± 10.4) treated with oral moxifloxacin with the indications of upper airway infections, community-acquired pneumonia, and acute exaggerated bronchitis were enrolled between January 2014 and September 2014. Local Ethical Committee has approved the study, and informed content was drawn from all participants. All patients were screened for cardiac arrhythmia before therapy (BT) (0^{th} day), on the 3^{rd} day (during therapy [DT]), and on the 10^{th} day (after therapy [AT]) with ECG and on the 3^{th} and 10^{th} day using Holter monitorization. Before starting of the therapy, the presence of structural heart disease was excluded using echocardiography. Other exclusion criteria were based on the laboratory tests. Antibiotic regimen was standardized to oral 400 mg moxifloxacin once daily for 7 days.

Exclusion criteria

- Known cardiac arrhythmias (atrial fibrillation, ventricular tachycardia, supraventricular tachycardia, ventricular ectopic beats, and atrial ectopic beats)
- Acquired/congenital long QT syndrome
- Left ventricular systolic dysfunction (ejection fraction [EF] <40%) and/or symptomatic heart failure
- Using QT/QTc prolonging drugs (Class IA and III antiarrhythmic drugs; tricyclic antidepressants), neuroleptics (e.g., phenothiazine, sertindole, and haloperidol), some antibiotics (e.g., halofantrine and pentamidine), and antihistaminics (e.g., therphenadine and astemizole)
- Severe heart valve stenosis and/or regurgitations (>2/4)
- Congenital heart diseases (e.g., mitral valve prolapses, hypertrophic cardiomyopathies, arrhythmogenic right ventricular dysplasia, and Brugada syndrome)
- Cardiopulmonary resuscitation
- Severe hypokalemia (<3.5 mmol/l), hyperkalemia (>5.5 mmol/l), hypercalcemia (>10.5 mg/dl), hypocalcemia (<8.5 mg/dl)
- <18 years of age
- Having other infections except upper and lower airway infections
- Using antibiotics for upper and lower airway infections except moxifloxacin
- Severe hepatic diseases (Child-Pugh Class C or aspartate aminotransferase (ACT) and/or alanine aminotransferase levels are higher 5 times above normal levels) and gallbladder diseases
- Having malignancy
- Thyroid diseases
- Pregnancy and/or breastfeeding period
- Using iron (Fe) preparations, antiacites
- Having allergy to moxifloxacin and other fluoroquinolones.

Transthoracic echocardiography was performed to all patients. The echocardiographic examination was performed at least 15 min after the rest using the GE Vivid 9 Expert (USA) device and the 3V2 transthoracic probe in the left lateral position (two-dimensional, color Doppler echocardiography) using parasternal and apical windows. Echocardiography was performed to each participant in accordance with the American Society of Echocardiography guidelines and the European Standard Echocardiography Guidelines.[11] The EF was calculated according to the modified Simpson's method. Echocardiography was performed and all results were evaluated by the same physician in all patients.

In our study, ECGs were obtained by 12-channel ECG devices using X Hewlett-Packard Pagewriter XLI (Philips, Germany), which is used by our cardiology department. The ECG images were performed by experienced technicians, and poor quality shots were repeated, and all shots were performed in supine position at a speed of 25 mm/s and a calibration of 10 mm/mV. At the time of recording, we tried to prevent speech, coughing, and excessive tremor which could affect the quality of the shooting. The rhythm, heart rate (HR), PR interval, QRS duration, and QT and QTc durations of all were evaluated by ECG. QTc time was calculated based on the Bazett formula. The longest QT time (QTmax) and the shortest QT time (QTmin) were determined in the 12-channel ECG and the QT dispersion (QTmax − QTmin) was calculated manually. All ECGs were evaluated by the physician who performed the study.

The laboratory parameters were studied from venous blood samplings before the initiation of the therapy. The evaluation

of the ECG and Holter monitoring was performed by the same researcher blinded to the other clinical and laboratory data.

Statistics

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL, USA). The normal distribution of the data was evaluated using Kolmogorov–Smirnov test. Those who exhibited normal distribution from numerical variables were shown as mean ± standard deviation, and those without normal distribution were shown as median with percentiles. Categorical variables were expressed as numbers and percentages. In the comparison of two categories, *t*-test (in numerical variables with normal distribution) and Mann–Whitney U-test (in nonnormally distributed numerical variables) were used in independent samples. Chi-square test and Fisher's exact test were used to compare the categorical data. Two-way ANOVA test was used for repeating samples, and Bonferroni corrected *t*-test was used for pair-wise comparisons in comparison of the pre- and post-treatment follow-up variables. The Bonferroni test was used as a *post hoc* test in the interaction of results with gender. Friedman test was used to compare the pretreatment and posttreatment 3rd and 10th day variables, and the Wilcoxon test with Bonferroni correction was used for bilateral comparisons. $P < 0.05$ was considered statistically significant.

Results

Forty-four patients (20 females and 24 males) were included into the study. The average age of the study group was 34.0 ± 10.4 years. In our study, all laboratory parameters were in normal range for all patients, and there was not any structural heart disease. Patient's demographics, laboratory

Table 1: Demographics, laboratory analyses, and echocardiographic findings

Variables	Population (*n*=44)	Female (*n*=20)	Male (*n*=24)	*P*
Baseline characteristics of patients				
Age	34.0±10.4	34.4±11.8	33.7±9.2	0.831
Body mass index (kg/m^2)	24.2±3.3	23.1±3.9	25.0±2.6	0.063
Smoking, *n* (%)	28 (63.6)	8 (40.0)	8 (33.3)	0.757
Laboratory findings				
Potassium (mmol/L)	4.4±0.5	4.3±0.5	4.6±0.5	0.110
Magnesium (g/dL)	2.1±0.3	2.2±0.2	2.1±0.3	0.398
Hemoglobin (mg/dl)	14.2±1.3	13.4±1.2	14.9±1.1	0.001*
WBC (10^3/µL)	8.1±2.3	7.9±2.1	8.3±2.4	0.557
Echocardiographic findings				
Aortic root (cm)	2.7±0.3	2.5±0.2	2.9±0.3	0.001*
Basal septal thickness (cm)	1.0±0.2	0.9±0.2	1.1±0.1	0.003*
Basal posterior wall thickness (cm)	1.0±0.2	0.9±0.2	1.0±0.1	0.004*
LV end diastolic diameter (cm)	4.3±0.4	4.1±0.4	4.5±0.3	0.004*
LV systolic diameter (cm)	2.7±0.3	2.6±0.3	2.8±0.3	0.033*
LA diameter (cm)	3.4±0.3	3.2±0.3	3.5±0.3	0.030*
RA diameter (cm)	3.1±0.3	3.0±0.3	3.3±0.2	0.001*
LV end-diastolic volume (ml)	77.8±14.2	70.1±10.8	84.2±13.7	0.001*
LV end-systolic volume (ml)	31.2±6.5	28.0±5.5	33.8±6.2	0.002*
EF (%)	59.9±2.8	60.5±3.2	59.4±2.3	0.182
M1 (cm/sn)	86.0±19.3	90.6±16.3	82.2±21	0.153
M2 (cm/sn)	67.8±13.7	66.6±13.4	68.8±14.2	0.611
T1 (cm/sn)	61.9±11.3	63.8±10.4	60.4±11.9	0.334
T2 (cm/sn)	50.6±11.8	51.2±13.4	50.1±10.6	0.769
A (cm/sn)	138.7±16.4	138.8±14.8	138.6±18	0.974
MR				
Minimal	18 (40.9)	10 (50.0)	8 (33.3)	0.231
1/4 MR	1 (2.3)	1 (5.0)	-	
TR				
Minimal	18 (40.9)	9 (45.0)	9 (37.5)	0.760
1/4 TR	-	-	-	
Aortic regurgitation	-	-	-	-
Pulmonary regurgitation	90.9±13.5	90.7±15.2	91.1±12.3	0.927
LV diastolic dysfunction				
Grade 1	5 (11.4)	1 (5.0)	4 (16.7)	0.356

*P<0.05 statistically significant. A: Aortic velocity M1: Mitral E velocity, M2: Mitral A velocity T1: Tricuspid E velocity T2: Tricuspid A velocity, MR: Mitral regurgitation, WBC: White blood cells, TR: Tricuspid regurgitation, LV: Left ventricular, RA: Right atrium, LA: Left atrium, EF: Ejection fraction

Table 2: Basal electrocardiography findings (0th day) and Holter findings during therapy (3rd day)

Variables	Population (*n*=44)	Female (*n*=20)	Male (*n*=24)	*P*
Basal ECG findings				
HR (beat/min)	80.3±13.9	78.9±13.5	81.5±14.5	0.536
QRS (msn)	87.9±9.2	85.0±7.8	90.3±9.7	0.055
PR (msn)	153.8±18.1	153.9±18.7	153.8±18	0.979
QT (msn)	353.1±24.6	352.8±24.5	353.4±25.2	0.935
QTc (msn)	396.4±20.2	399.4±26.0	393.9±14.0	0.378
QTmax (msn)	379.5±24.5	378.0±24.8	380.8±24.7	0.707
QTmin (msn)	339.3±21	340.0±20.0	338.8±21.7	0.846
QTd (msn)	39.8±15.5	37.0±16.6	42.1±14.4	0.283
Holter findings during therapy (3rd day)				
HRmin (beat/mn)	56.0±7.3	56.6±4.4	55.6±9.1	0.681
HRmax (beat/mn)	123.7±14.7	128.3±15.1	119.9±13.5	0.057
SVES	170 (0-691)	11 (0-19)	155 (0-691)	0.909
VES	453 (0-4412)	152 (0-370)	854 (0-4412)	0.457
Sinus rhythm (%)	44 (100)	20 (100)	24 (100)	

HR: Heart rate, HRmax: Maxımum heart rate, HRmin: Minimum heart rate, QTc: Corrected QT, SVES: Supraventricular extrasystole, VES: Ventricular extrasystole, ECG: Electrocardiography

analyses, and echocardiographic findings are presented in Table 1. Baseline ECG measurements including HR, QRS, PR, QT, QTc, QTmax, QTmin, and QTd as well as Holter findings including HRmax, HRmin, supraventricular extrasystole (SVES), and ventricular extrasystole (VES) DT are also presented in Table 2. Accordingly, there are no differences between male and gender patients. When the ECG findings BT, DT, and AT were evaluated together in the entire population [Table 3], HR was diminished DT and AT compared to baseline, QT was prolonged DT and AT, but QTc was only prolonged DT. QRS, PR, and QTd parameters were all similar between the groups. On the other hand, when ECG findings BT, DT, and AT were analyzed according to gender [Table 4 and Figure 1], in female patients, but not in male ones, QT distance was prolonged significantly DT and AT (*P* interaction = 0.031). The decrease in HR was significant in males DT and AT (*P* interaction = 0.036), and QTc changes BT, DT, and AT remained similar between male and female patients (*P* interaction = 0.890). QRS, PR, and QTd measurements were comparable between the groups in terms of gender. The comparison of Holter findings DT and AT including HRmax, HRmin, SVES, and VES revealed similar findings [Table 5] which was not affected by the gender [Table 6].

Table 3: Electrocardiography findings before therapy, during therapy (3rd day), and after therapy (10th day)

Variables	Before therapy	3rd day	10th day	*P*
HR (beat/min)	80.3±13.9	76.3±11.3[ŧ]	75.9±10.6[ŧ]	0.034*
QRS (msn)	87.9±9.2	87.7±8.5	88.5±9.4	0.717
PR (msn)	153.8±18.1	156.8±19.3	156.5±18.8	0.400
QT (msn)	353.1±24.6	363.3±23.7[ŧ]	361.8±20.8[ŧ]	0.007*
QTc (msn)	396.4±20.2	404.4±19.3[ŧ,§]	397.5±21.0	0.011*
QTmax (msn)	379.5±24.5	395.5±27.6[ŧ]	395.0±32.6[ŧ]	0.001*
QTmin (msn)	339.3±21.0	352.7±25.6	349.6±27.1[ŧ]	0.008*
QTd (msn)	39.8±15.5	45.5±18.0	45.9±20.5	0.183

[ŧ]There is significant difference before therapy ($P<0.05$), [§]There is significant differences after therapy ($P<0.05$), *$P<0.05$ statistically significant, *P* (int): *P* interaction: The effect of the factor of gender during therapy and after therapy, HR: Heart rate, QTc: Corrected QT, QTd: QTmax − QTmin

Discussion

In our study, we have demonstrated that oral moxifloxacin therapy for the indication of airway infections resulted in a temporary increase in QT interval DT. However, it does not affect QTc and is not related with serious cardiac arrhythmias during Holter monitoring.

It is well known that oral moxifloxacin prolongs the QT/QTc interval. However, there are very few case reports, preclinical studies, and clinical trials of moxifloxacin-related TdP.[12-14] The presence of additional risk factors (such as other drug use) that prolong the QT interval is thought to be an important predisposing factor for TdP development in these reported cases.

The effect of moxifloxacin on QT interval is reversible and dose related. It effects weakly but rapidly activated rectifying potassium channel blockade, IKr[3] or HERG potassium channels.[4] Retrospective data suggested an increase in cardiac event rates with moxifloxacin use.[12] Nevertheless, except for case reports and experimental trials about QT/QTc, there are insufficient data in the literature on the incidence of cardiac arrhythmias detected by ECG and Holter monitoring. In one of the previous prospective studies investigating the influence of quinolone drugs on QT and TdP development, QT interval was shown to prolong about 6 ms as compared to baseline values; however, TdP did not occur after 7 days of single-dose moxifloxacin use among healthy individuals with a mean age of 34 years, who did not have any cardiovascular or renal diseases, who were not using any drugs that could be effective on QT.[15] Similarly, we detected a 10.2 ms increase in QT interval under

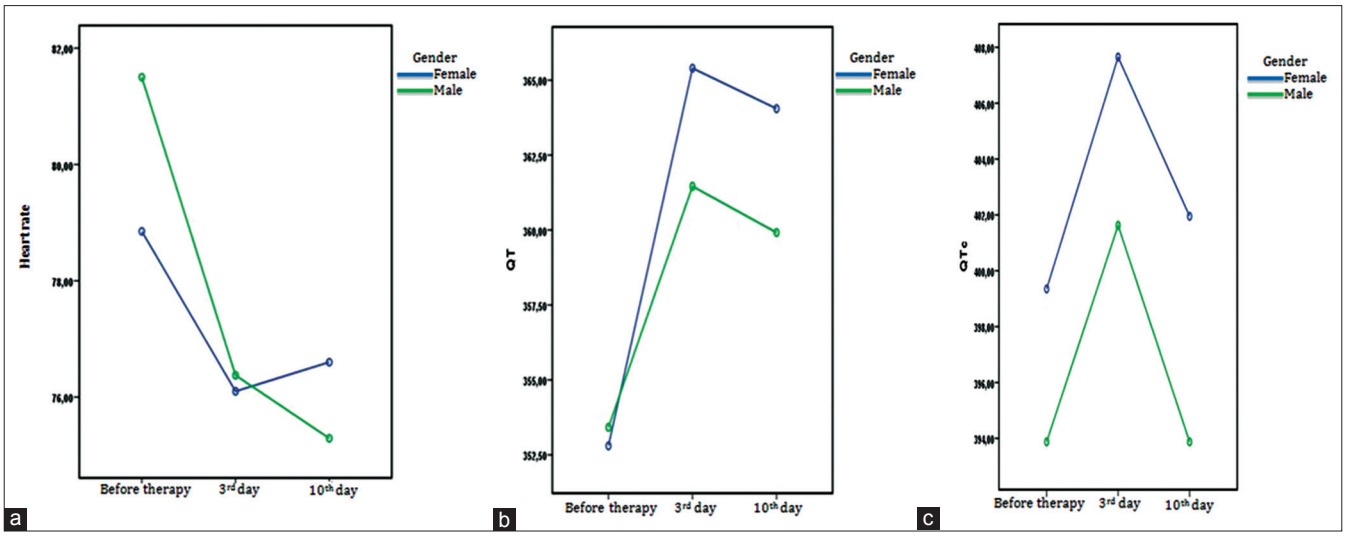


Figure 1: (a-c) Heart rate, QT and QTc, changes before during and after antibiotherapy according to genders

Table 4: Electrocardiography findings before therapy, during therapy, and after therapy according to gender

Variables	Gender	Beforetherapy	3rd day	10th day	*P*	*P* (int)
HR (beat/min)	Female	78.9±13.5	76.1±11.8	76.6±11.7	0.506	0.036*
	Male	81.5±14.5	76.4±10.6	75.3±9.9	0.038‡	
QRS (msn)	Female	85.0±7.8	83.9±7,0	84.6±6.6	0.741	0.635
	Male	90.3±9.7	90.8±8.5	91.8±10.1	0.627	
PR (msn)	Female	153.9±18.7	157.0±18.6	155.6±19.4	0.786	0.906
	Male	153.8±18.0	156.8±20.2	157.3±18.7	0.367	
QT (msn)	Female	352.8±24.5	365.4±25.7	364.1±20.6	0.022‡	0.031*
	Male	353.4±25.2	361.5±22.4	359.9±21.2	0.212	
QTc (msn)	Female	399.4±26.0	407.7±19.8	402.0±22.0	0.262	0.890
	Male	393.9±14.0	401.6±18.8	393.9±19.8	0.116	
QTd (msn)	Female	37.0±16.6	46.0±18.5	50.0±18.9	0.082	0.236
	Male	42.1±14.4	45.0±17.9	42.5±21.5	0.797	

HR: heart rate, QTc: corrected QT , QTd: QTmax- QTmin, ‡significant differences were shown between "before therapy-3rd day" and before therapy-10th day", **P* (int): *P* interaction: the effect of gender factor during therapy and after therapy

Table 5: Holter findings during therapy and after therapy

Variables	3rd day	10th day	*P*
HRmin (beat/min)	56.0±7.3	55.5±6.5	0.587
HRmax (beat/min)	123.7±14.7	126.8±15.4	0.089
SVES	170 (0-691)	220 (0-413)	0.589
VES	453 (0-4412)	752 (0-3377)	0.517

HR: Heart rate, HRmax: Maximum heart rate, HRmin: Minimum heart rate, SVES: Supraventricular extrasystole, VES: Ventricular extrasystole

treatment, and an 8.5 ms increase was detected after treatment compared to baseline values. In our study, QTc interval was detected to increase 8 ms during treatment (on day 3) compared to pretreatment value (day 0); however, it returned to almost pretreatment values after treatment (on day 10). We considered that the detection of prolonged QTc interval after treatment (on day 10) might be associated with higher HR at the beginning (the difference was 5 beats per minute [BPM]) of moxifloxacin therapy. When evaluated with regard to QTc intervals, only 1.1 ms difference was observed between day 0 and 10. In our study, QTc interval did not prolong to cause TdP. In another randomized, double-blind, placebo-controlled study, an QTc prolongation of 4.0% ± 5.1% was observed at 2 h after oral administration of 400 mg/day moxifloxacin in young and healthy cardiac patients, but TdP did not develop in any of them. In the same study, a QTc prolongation of 4.0% ± 5.1% was observed when 800 mg oral moxifloxacin was given daily, but no development of TdP was observed.[16]

Holter ECG was performed to detect drug-induced arrhythmias after initiation of oral moxifloxacin in all patients. In previous studies, Holter ECG was performed on the 1st day of moxifloxacin treatment (3 h after initiation of the therapy). In our study, we decided to perform the first Holter ECG on the 3rd day, because the stable peak effect of oral moxifloxacin (also on QT/QTc) is shown to be on the 3rd day. Furthermore, the other reasons are that the patients are being treated remotely and the antibiotics cannot be taken on the day they are prescribed. For these reasons, we applied Holter and ECG procedures on the 3rd day. There are also animal studies and experimental studies in the literature where QT/

Table 6: Holter findings during therapy and after therapy between genders

Variables	Gender	3rd day	10th day	*P*	*P* (int)
HRmin (beat/min)	Female	56.6±4,4	56.2±5.8	0.765	0.908
	Male	55.6±9,1	55.0±7.1	0.657	
HRmax (beat/min)	Female	128.3±15.1	131.2±14.9	0.368	0.879
	Male	119.9±13.5	123.2±15.3	0.131	
SVES	Female	11 (0-19)	24 (0-52)	0.333	0.340
	Male	155 (0-691)	220 (0-413)	0.377	
VES	Female	152 (0-370)	314 (0-862)	0.333	0.247
	Male	854 (0-4412)	752 (0-3377)	0.302	

HR: Heart rate, HRmax: Maximum heart rate, HRmin: Minimum heart rate, SVES: Supraventricular extrasystole, VES: Ventricular extrasystole, *P* (int): *P* interaction: The effect of the factor of gender during therapy and AT, AT: After therapy

QTc, QT dispersion calculations with telemetric follow-up after oral moxifloxacin, and similar results in terms of QTc and QT dispersion prolongation and no TdP formation are observed.[17,18]

QT dispersion is a gross and estimated measurement of repolarization abnormalities of myocardium; in addition, severe concerns exist about the accuracy of estimation methods.[19,20] All values which have been suggested as upper limit in healthy individuals were noticed not to be safe.[21-23] Therefore, abnormal QT dispersion values in the literature (>100 ms) out of the error limits are suggested to have clinical importance for indicating repolarization abnormality. In our study, we did not detect a difference in QT dispersion values during (on day 3) and after (on day 10) treatment compared to pretreatment values ($P > 0.05$). A statistically significant difference was not observed between genders when QTd interval was evaluated before, during, or after treatment ($P > 0.05$). Before treatment, QTd interval was measured on an average of 37.0 ms in females and 42.1 ms in males. During treatment, these values were found as 46 ms and 45 ms, respectively, for females and males. After treatment, QTd was measured as 50 ms in females and 42.5 ms in males. The differences in QTd before, during, or after treatment were not found statistically significant ($P = 0.236$), and all of these values were within the QT dispersion interval seen in healthy individuals reported in the literature (10–71 ms).

The mean HR assessed by Holter monitoring was not significantly different during and after antibiotic therapy. However, the mean HR measured from surface ECG was significantly reduced during and after antibiotic therapy compared to baseline (BT: 80.3 ± 13.9 BPM vs. DT: 76.3 ± 11.3 BPM vs. AT: 75.9 ± 106 BPM; $P = 0.007$). Since the patients admitted to the hospital had fever leading to tachycardia, the HRs of the patients were reduced during and after antibiotic therapy. When the Holter monitoring findings of our study were analyzed in terms of gender interaction, minimal and maximal HR, QT dispersion parameters, as well as the frequencies of VES and SVES, and other arrhythmia findings were not different between male and females. Mean QT interval value was increased on the 3rd day when compared to 0th day and was similar with the value on the 10th day (BT: 353.1 ± 246 msn vs. DT: 363.3 ± 23.7 msn vs. AT: 361.8 ± 20.8 msn; $P = 0.034$). Mean QTc interval was significantly increased on the 3rd day but was decreased to the baseline value (BT: 396.4 ± 20.2 msn vs. DT: 404.4 ± 19.3 msn vs. AT: 397.5 ± 21.0 msn; $P = 0.011$).

Conclusion

Four hundred milligrams of oral moxifloxacin started on an outpatient basis due to indications of upper and/or lower airway infections results in an increase in QT interval DT. However, it does not affect QTc to critically increased values (>500 msn) and is not related to serious cardiac arrhythmias during Holter monitoring.

Strengths and limitations

The relatively small number of the patients in this study is the most important limitation which precluded adjustment of our results to the general population. Our study has included patients on an outpatient basis. If we were able to add hospitalized patients, we could calculate QT/QTc and other arrhythmia parameters under telemetric or continuous ECG monitoring. Since the dose of oral moxifloxacin was kept constant at 400 mg/day, we could not have any information if any QT/QTc duration changes might occur in patients treated with 400 mg bid. On the other hand, our study has some strength. First, there is not adequate number of clinical data evaluating the possible arrhythmogenic effects of this antibiotic. Second, we did not any drop out during the follow-up period, and all symptoms and any possible changes on the ECG and Holter were carefully and closely monitored. We hope that our study will inspire further clinical studies on this issue.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Broken Coronary Stent Catheter Retrieval Percutaneously Case Report and Literature Review

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Abstract

We present a 73-year-old male patient with an unusual complication of a broken coronary stent catheter during percutaneous coronary angioplasty, which was successfully retrieved by balloon trapping and pulling-back method, along with literature review of similar cases.

Keywords: Coronary stent catheter break, percutaneous coronary intervention, percutaneous retrieval

Introduction

As interventional cardiology era has been improving and advanced percutaneous coronary interventional procedures have been increasingly performed worldwide, operators might be confronted with some complications. We report a case of coronary stent delivery catheter breaks and its successful retrieval, and we review the literature in this regard.

Case Report

A 73-year-old male patient was admitted to the emergency department with unstable angina pectoris. After his medical therapy was initiated, diagnostic coronary angiogram was performed. Coronary angiogram revealed a critical stenosis of obtuse marginal branch of the left circumflex artery. Percutaneous intervention to the obtuse marginal branch of the left circumflex artery was mandatory.

The procedure started with punction of the left common femoral artery, which was extremely tortuous. After obtaining a successful vascular access, the left main coronary artery was cannulated by a 6-French (6F) EBU guiding catheter (Medtronic Inc., Minneapolis, MN, USA). The patient was anticoagulated by administration of 100 U/kg unfractional heparin (UFH). Then, the operator passes through the critical stenosis by instrumentality of a soft 0.014-inch CHOICE floppy coronary guidewire (Boston Scientific, Marlborough, MA, USA). Subsequently, the critical stenotic lesion was predilated successfully with a 2.0 mm × 20 mm predilation balloon (Invader, Alvimedica Medical Technologies, Turkey) at 12 atmospheric (atm) pressure. Following successful predilation, the operator decided to proceed to the next step, which was implantation of a drug-eluting coronary stent (PROMUS Element, Boston Scientific, Marlborough, MA, USA). Although the whole delivery catheter was inside the guiding catheter, the stent did not reach the critical lesion.

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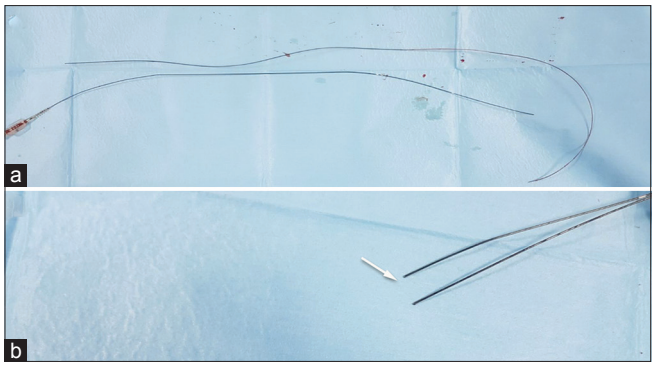


Figure 1: (a) Two broken parts of the whole coronary stent catheter. (b) The site of catheter break (white Arrow)

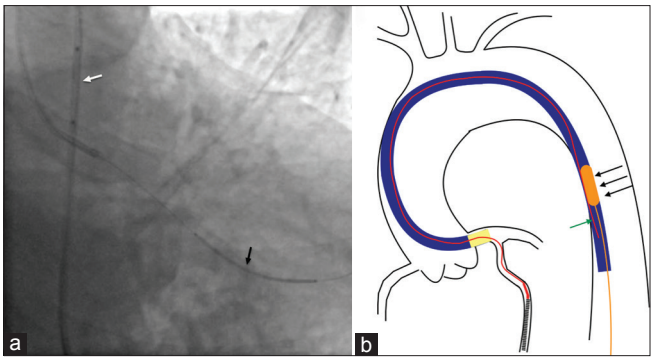


Figure 2: (a) Coronary angiogram view of broken stent delivery catheter in the coronary vasculature. Black arrow shows the coronary stent in the left circumflex artery. Trapping balloon (white arrow) traps the proximal half of the broken catheter. (b) The illustration of the technique. The proximal part of the broken stent catheter (green arrow). Broken catheter is trapped by inflation of balloon (black arrow)

Suddenly, it was realized that while it was pushed forward, the delivery catheter broke into halves in the guiding catheter because of the extremely tortuous vascular access. One of the broken parts of the delivery catheter was totally inside the body, and the other part was partially in the guiding catheter and its hub was out of the guiding catheter. The operator pulled back the distal part of the broken delivery catheter out of the body [Figure 1]. After that, a 2.5 mm × 20 mm coronary predilation balloon catheter (Invader, Alvimedica Medical Technologies, Turkey) was inserted into the guiding catheter and passed by the proximal half of the broken stent delivery catheter. By the help of inflation coronary balloon inside of the guiding catheter, the broken part of the stent delivery catheter was trapped inside of the guiding catheter between the predilation balloon and the guiding catheter wall [Figure 2]. It was achieved by withdrawal of the broken part of stent delivery catheter into the guiding catheter by trapping and pulling back the inflated predilation balloon repetitiously [Figure 2]. Just after being sure that the broken part of the catheter was totally in the guiding catheter, all the system was pulled out of the body. After the successfully management of this complication, the left main coronary artery was engaged by a new EBU guiding catheter (Medtronic Inc., Minneapolis, MN, USA). The procedure was continued by crossing the critical stenotic lesion. Finally, a 3.0 mm × 38 mm drug-eluting coronary stent (PROMUS Element, Boston Scientific, Marlborough, MA, USA) was implanted successfully, and the procedure was terminated without any complication.

Discussion

Inadvertent retention of coronary hardware such as guidewire, stent or balloon delivery catheter, distal part of atherectomy devices, or dislodged coronary stents due to entrapment or catheter break is very uncommon complication, which leads to myocardial ischemia or infarction, vascular tissue injury, and even death, during percutaneous coronary interventions. Management of such complication requires additional intervention such as surgical or percutaneous intervention. There are several established several retrieval methods for overcoming this unwanted complication with regard to percutaneous intervention. These methods can be summarized as small balloon technique, two-wire technique, snares, forceps, retrieval baskets, specific retrieval devices, and distal embolic protection devices.[1] Despite these well-established techniques, compensation for such complication can be very challenging sometimes.

In the literature, there are several case reports, including different clinical scenario and various implementation of retrieval technique [Table 1]. Wani *et al*.[2] reported a case of stent delivery catheter break during percutaneous coronary angioplasty. In this case, the complication was successfully managed by compression of the fractured part of the delivery catheter in the guiding catheter by balloon trapping and removing the entire system out of the body. In the literature, there are several similar cases.[4,6,7,13-15] Another retrieval method was mentioned by Chan *et al*.[3] In the course of balloon dilation of side branch ostium after main vessel stent deployment, the shaft of balloon catheter accidentally broke, and Chan *et al*. retrieved the broken part of the catheter by means of using an alligator forceps. An alternative approach for retrieval the foreign bodies in coronary circulation is balloon-supported catheter-assisted retrieval technique. Kunwar *et al*.[5] made a success of restraining of the broken part of balloon catheter between guiding catheter and dilation balloon, followed by ensheathing this broken part into the guiding catheter. A relatively simple method, which was gently withdrawing the entire system as a unit without any additional technique was applied by O'Neill *et al*.[9] In another complicated case, after failed attempts by using snare, two-wires and balloon techniques to remove a broken intravascular ultrasound catheter in the coronary vasculature, Chang *et al*.[12] achieved to remove it by the help of using distal embolic protection device. Vimal Mehta *et al*.[11] achieved to retrieve the distal portion of a broken thrombectomy catheter by means of guiding catheter-supported balloon inflation and pulling-back technique. Similar problems might emerge during advanced percutaneous coronary interventions as well. Imamura *et al*.[10] reported a case of Rotablator® (Boston Scientific,

Table 1: Literature review of retrieval methods

Case	Author	Journal	Publication year	References	Retrieval method
1	Wani *et al*.	Korean Circulation Journal	2010	[2]	Balloon trapping and pulling back whole assembly
2	Chan *et al*.	Catheterization and Cardiovascular Interventions	1999	[3]	Alligator forceps grasping
3	Kharge *et al*.	*Texas Heart Institute Journal*	2012	[4]	Balloon trapping and pulling back whole assembly
4	Kunwar *et al*.	*Journal of Clinical and Diagnostic Research*	2017	[5]	Balloon-supported catheter-assisted retrieval technique
5	Kayaert *et al*.	Cardiovascular Revascularization Medicine	2013	[6]	Balloon trapping and pulling back whole assembly
6	Trehan *et al*.	Catheterization and Cardiovascular Interventions	2003	[7]	Balloon trapping and pulling back whole assembly
7	Gürbüz *et al*.	Turk Kardiyol Dern Ars	2015	[8]	Balloon-assisted loop snare retrieval
8	O'Neill *et al*.	*BMJ Case Reports*	2015	[9]	Traction whole system without using additional tool
9	Imamura *et al*.	Cardiovascular Intervention and Therapeutics	2017	[10]	Retrieval of a trapped burr using a balloon and Guideliner®
10	Mehta *et al*.	The International Journal of Angiology	2013	[11]	Catheter-assisted balloon inflation and pulling back
11	Chang *et al*.	International Heart Journal	2009	[12]	Retrieval with embolic protection device
12	Mehta *et al*.	Cardiovascular Intervention and Therapeutics	2014	[13]	Balloon trapping and pulling back whole assembly
13	León Jiménez *et al*.	Catheter Cardiovascular Intervention	2017	[14]	Balloon trapping and pulling back whole assembly
14	Fanari *et al*.	Cardiovascular Revascularization Medicine	2015	[15]	Balloon trapping and pulling back whole assembly

Marlborough, MA, USA) driveshaft fracture and retrieval of entrapped burr by means of squeezing between inflated balloon and GuideLiner® (Japan Lifeline, Tokyo, Japan) and pullback into the guiding catheter.

Sometimes, operators can be encountered similar complications during percutaneous peripheral vascular interventions. Gürbüz *et al*.[8] experienced and reported such a complication which occurred after peripheral vascular intervention. In this case report, a broken self-expandable peripheral stent cateheter was retrieved succesfully by a techique which icluded a loop snare combined with an inflated balloon.

Consequently, until recently, several retrieval methods have been applied, but none of these methods are like our retrieval technique. On the basis of literature review, our technique, which is balloon trapping and withdrawing the broken hardware and getting it into the guiding catheter before pulling back the whole system, is a unique technique and till now this method is never reported in the interventional era. This method might be safer than other techniques because the broken catheter is completely in the guiding catheter while pulling all systems out of the body. Finally, this method should always be kept in mind in case of a similar complication.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

The de Winter Electrocardiographic Pattern: What Else do we need to Learn?

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Abstract

Electrocardiographic (ECG) abnormalities are often indicative of acute coronary artery occlusion. Early detection of these abnormalities is important for the identification of patients who may be candidates for emergent percutaneous coronary revascularization (PCR). In most cases, ST-segment elevation is the key factor in selecting patients for PCR. However, some cases with acute coronary artery occlusion do not have ST-segment elevation, resulting in delays in coronary reperfusion treatment. A 37-year-old male presented to the emergency department with typical chest pain. The patient indicated that he was a heavy marijuana user. Even though his admission ECG did not reveal ST-segment elevation, he was hemodynamically stable, and he did not develop life-threatening arrhythmias, he was immediately taken to the catheterization laboratory for urgent angiography with the diagnosis of acute myocardial infarction. The occluded left anterior descending artery seen in angiography was successfully revascularized with percutaneous coronary intervention. Herein, we present a case of a patient who was admitted to the emergency department with chest pain and ECG demonstrating the de Winter pattern. Based on this case, we present a detailed evaluation regarding the de Winter ECG pattern, which is equivalent to ST-segment elevation.

Keywords: Acute left anterior descending coronary artery occlusion, de Winter pattern, electrocardiography, primary percutaneous coronary intervention

Introduction

In the absence of overt ST-segment elevation, there are several other electrocardiographic (ECG) patterns that can indicate a need for emergent revascularization. The literature terms these patterns as ST-elevation myocardial infarction (STEMI) equivalents.[1] The present case illustrates the importance of recognizing the de Winter ECG pattern as a STEMI equivalent in cases with suspected acute myocardial infarction. The current guidelines indicate ST-segment elevation as the primary indication for emergent revascularization. However, as a STEMI equivalent, the de Winter ECG pattern is equally important and should be promptly recognized in the emergency department as it indicates an immediate need for emergent revascularization.

Case Report

A 37-year-old male with no previous medical history presented to the emergency department with typical chest pain for 2 h. He said that he had been using marijuana two times/day for the past 10 years. On admission, his arterial blood pressure was 125/75 mmHg, and his heart rate was 74 bpm. Electrocardiography revealed marked ST-segment

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depression of up to 2 mm after the J point, hyperacute T-waves in derivations V3-V6, and ST-segment depression of 0.5 mm in the inferior leads [Figure 1]. After being given a loading dose of clopidogrel (600 mg) and acetylsalicylic acid (300 mg), he was taken to the catheterization laboratory for emergent coronary angiography. Angiography revealed a 98% thrombotic stenosis at the proximal portion of the left anterior descending artery (LAD) [Figure 2a] and plaques in the circumflex and right coronary arteries without significant stenosis. Therefore, following a bolus dose (10 μg/kg) of intravenous (IV) tirofiban, the patient successfully underwent balloon angioplasty (Invader 2 mm × 15 mm, 16 atm) with stenting (drug-eluting stent, Biomatrix 2.75 mm × 24 mm, 10 atm) [Figure 2b and Video 1]. The patient was then transferred to the coronary care unit, where he received IV tirofiban infusion (0.1 μg/kg/min). An ECG recorded 90 min after the coronary revascularization revealed a sinus rhythm with complete resolution of the de Winter ECG pattern [Figure 3]. No bleeding, thrombotic, or ischemic events occurred during the hospitalization, and the patient was discharged from the hospital after 7 days.

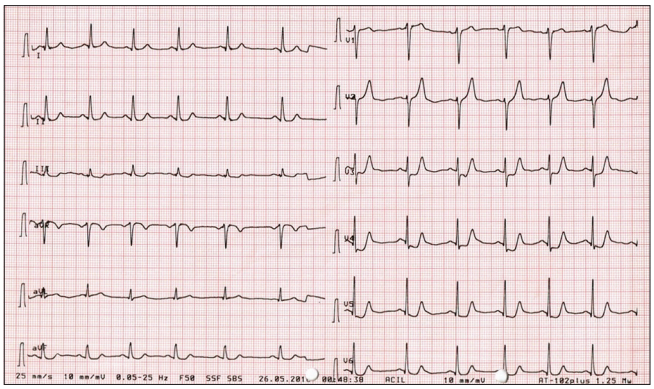


Figure 1: Electrocardiographic obtained in the emergency department showing marked ST-segment depression in leads V3-V6 and tall, symmetrical T-waves in the precordial leads

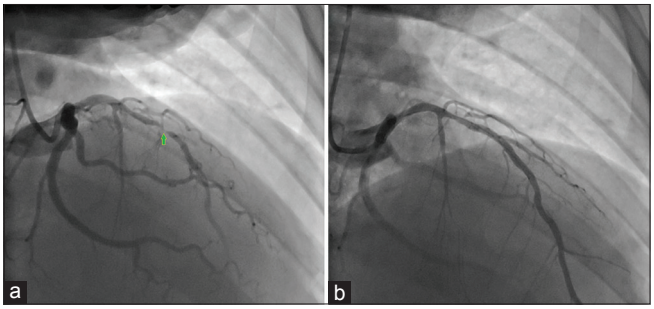


Figure 2: Selective left coronary angiography before (a) and after (a) emergent percutaneous coronary intervention. Coronary angiography showing subtotal occlusion at the proximal segment of left anterior descending (a). Coronary angiography showing left coronary artery after successful reperfusion followed by stent placement (b)

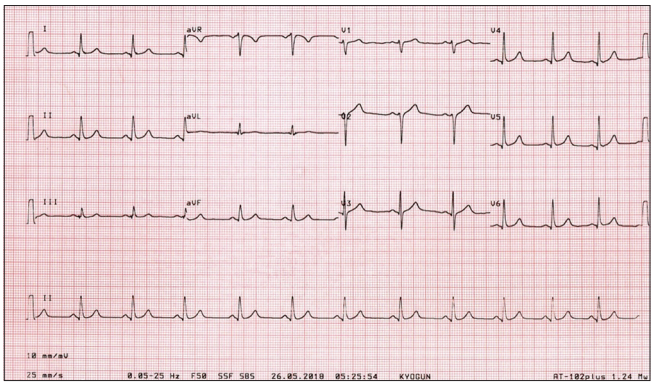


Figure 3: Electrocardiographic 90 min after coronary revascularization (left anterior descending stenting) showing resolution of the de Winter electrocardiographic pattern

Discussion

The eponymous ECG pattern was first described in 2008 by de Winter *et al*. in 2% of patients with acute anterior wall myocardial infarction.[2] In 2009, Verouden *et al*. demonstrated the de Winter ECG pattern in 35 of 1890 patients who underwent primary percutaneous coronary intervention (pPCI) for LAD artery obstruction.[3] The de Winter ECG pattern consists of persistent 1–3-mm ST-segment depression at the J-point, upsloping ST segments that continue into tall, symmetrical T-waves in the precordial (V1-V6) leads, and slight ST-segment elevation in augmented vector right (aVR). In addition, ST-segment depression in the inferior leads is frequently seen in the de Winter ECG pattern. This pattern has positive predictive values of 95%–100% in the respective diagnostic studies.[4] As in the case described herein, patients with the de Winter ECG pattern are generally younger and more often male. Despite the presence of persistent LAD occlusion, it was initially thought that de Winter ECG pattern was a static condition that did not evolve into overt ST-segment elevation.[2,3] However, it was later described that de Winter ECG pattern could evolve into ST-segment elevation in anterior derivations (consistent with STEMI) prior to coronary revascularization.[4,5] On the other hand, Zhao *et al*. described two ECG patterns indicating that ST-segment elevation can evolve into the de Winter ECG pattern.[6] Montero-Cabezas *et al*. indicated that Q-wave and/or ST elevation may occur in ECGs performed after successful coronary revascularization.[7] Finally, in 2018, Tsutsumi and Tsukahara demonstrated the de Winter ECG pattern in the inferiolateral (II, III, aVF, and V4-V6) leads in a patient who underwent pPCI for right coronary artery obstruction.[8] In the present case, the ECG recorded 90 min after successful coronary reperfusion revealed loss of the de Winter pattern without ST elevation. In light of the current case and published data, we believe that the de Winter ECG pattern can be divided into two subgroups as follows: (1) static pattern characterized by a J-point depression that persists until coronary revascularization and does not evolve into overt ST-segment elevation and (2) dynamic pattern that can evolve into ST-segment elevation (or vice versa) in the context of total occlusion or spontaneous recanalization.[3,7]

The exact electrophysiological mechanisms underlying these ECG changes are not exactly known. However, it has been hypothesized that defective sarcolemmal adenosine triphosphate-sensitive potassium channel activation is responsible for the absence of ST-segment elevation.[9,10] Another potential explanation is an anatomical variant of the Purkinje fibers with endocardial conduction delay. Moreover, some authors postulated that collateral blood supply might protect the myocardium from transmural ischemia and prevent ST-segment elevation, and others advocated that the area of transmural ischemia was so large that no injury currents were generated toward the precordial leads but only directed upward to an aVR lead.[8]

Conclusion

The de Winter ECG pattern is important to recognize because it is associated with subtotal or total obstruction of the proximal segment of the LAD artery and is considered a STEMI equivalent. Therefore, ambulance staff, emergency physicians, and cardiologists should be able to recognize the de Winter ECG pattern in addition to other ECG patterns that are considered to be STEMI equivalents, including Wellens syndrome, posterior ST-elevation myocardial infarction, Sgarbossa criteria in left bundle branch blocks, and ST elevation in lead aVR. We emphasize that although the current revascularization guidelines highlight ST-segment elevation as the principle indication for emergent revascularization, the de Winter pattern should also be recognized without delay, as it implies the same indications as ST-segment elevation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Thrombus on the Device Early After the Procedure of the Left Atrial Appendage Closure with the Amplatzer Cardiac Plug: Is Something Wrong with the Procedure or the Device?

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Abstract

Percutaneous left atrial appendage (LAA) closure is a currently utilized procedure for the prophylaxis of thromboembolic cerebrovascular events in selected patients with nonvalvular atrial fibrillation. The presence of thrombus on closure device was reported at 1st and 3rd months after the procedure, but as far as our knowledge, there are no data about early thrombus formation on the device during procedure. We present a case demonstrating thrombus on the atrial side of the Amplatzer Amulet LAA occluder device early after the implantation.

Keywords: Atrial fibrillation, sol atrial appendage, stroke

Introduction

Today, with an aging population, atrial fibrillation (AF) is more common and has an increased risk of embolic cerebrovascular accidents. Anticoagulation strategies alone are not sufficient, and as a large proportion of the thrombus involved in these cerebrovascular accidents are seen to arise from the left atrial appendage (LAA). Device closure of the LAA is a nonpharmacologic approach to stroke prevention in AF patients. We present a case with an early thrombotic complication during LAA closure which was successfully treated.

Case Report

A physically active 76-year-old female with persistent AF was referred for the LAA occlusion because of recurrent cerebral stroke, under anticoagulant therapy with warfarin and afterward with dabigatran 150 mg bid. The patient's CHADS-VASc score was 5 and HAS-BLED score was 3. After a multidisciplinary interrogation (neurologist, cardiologist, and radiologist), the cerebral stroke was attributed to thromboembolization secondary to AF and percutaneous LAA closure was planned. The patient's eligibility for treatment with the Amplatzer Amulet device was determined by cardiac computed tomography angiography and transesophageal echocardiography (TEE). The procedure was performed

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under general anesthesia, TEE, and fluoroscopic guidance. Transseptal access was achieved through the right femoral vein, using an SL1 sheath and a BRK-1 needle (St. Jude Medical, MN, USA). Intravenous heparin was given with a target activated clotting time >300s. An extra-stiff wire was advanced through the upper pulmonary vein, and then, we inserted a 14 F guiding sheath through the wire. Then, we inserted a 22 no device through the catheter, and we pulled back all system from the pulmonary vein and directed to the LAA ostium. We rotated the system counter-clockwise and positioned it into the LAA. We checked its position with fluoroscopy, two-dimensional (2D) and three-dimensional (3D) TEE. After we released the device, we recognized a linear thrombus on the atrial side of the device with 2D and 3D echocardiography [Figures 1 and 2]. We pulled back the catheter and there was a big linear thrombus on the distal tip of the catheter [Figure 3]. The activated clotting time (ACT) was 290 s at that time. We injected 5000 U unfractionated heparin (UFH) (intravenous) bolus after the procedure and continued with infusion at a rate of 1000 U/h for 48 h (dosage titrated according to activated partial thromboplastin time). After the infusion we performed TEE again and the thrombus had successfully been dissolved [Figure 4]. The patient was discharged with clopidogrel 75 mg 1 × 1 and acetylsalicylic acid 100 mg 1 × 1. One month after this procedure, TEE confirmed a good position of the device without thrombus [Figure 5].



Figure 1: 2D views of the thrombus on the device



Figure 3: Thrombus on the tip of the catheter

Discussion

In the literature, thrombus formation on the device was demonstrated at the 1st and 3rd months after the procedure.[1,2] However, there are no data about thrombus formation early after percutaneous LAA closure. Screw area of the device could be a progenitor of thrombus formation so we should be aware of giving effective dosage of UFH and obtaining at least 300s of ACT level during operation. Wolff *et al*.[3] recently reported two cases with early thrombus formation during Mitraclip procedure which were successfully treated with low dose thrombolytic infusion and with no embolic complication, but data about this kind of therapy particularly thrombi in the left side of the heart insufficient for us; hence, we choose the safer way.

Conclusion

This case demonstrates a management option of early thrombotic complication during LAA closure.

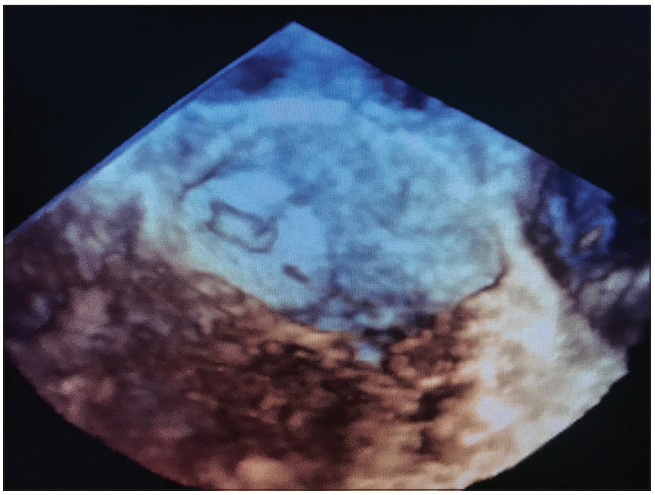


Figure 2: 3D views of the thrombus on the device

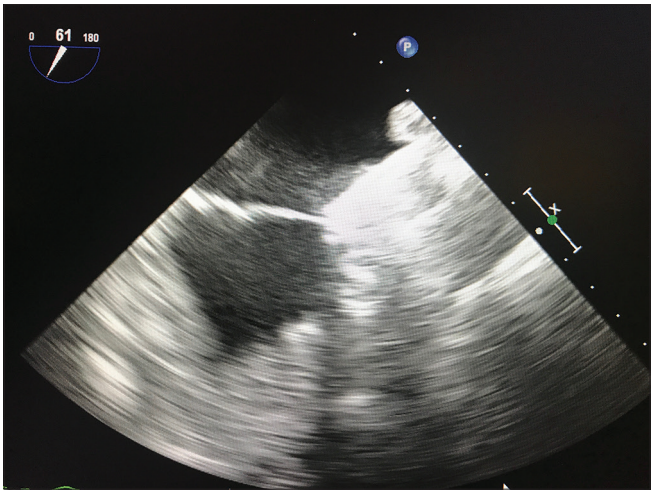


Figure 4: 2D view of the device after heparin infusion

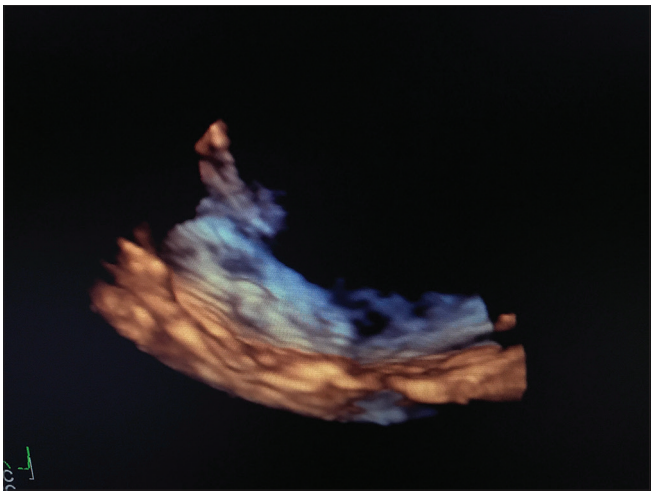


Figure 5: 3D view of the device after heparin infusion

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Conflicts of interest

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