

Suppression of refractory electrical storm by microtubule destabilization and dechanneling therapy in a patient with heart failure with reduced left ventricular ejection fraction and implantable cardioverter-defibrillator: A novel therapeutic approach

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Abstract

We investigated the impact of microtubule destabilization and dechanneling therapy on a suppression of refractory electrical storm (ES) in a 63-year-old male patient with ischaemic heart failure with reduced left ventricular ejection fraction (HFrEF), who had a history of previous coronary artery bypass grafting and implantable cardioverter-defibrillator (ICD). We have implemented 0.5mg (a low-dose) adjuvant colchicine once daily with a view to preventing ES of the patient in addition to conventional medication. This should ensure the microtubule destabilization and the pharmacological scar dechanneling because ES of the patient's resistance to conventional pharmacological treatment and multiple antiarrhythmic interventions (ATP). Seventy-two hours later, cardiac rhythm returned to sinus rhythm. In the subsequent follow-up, the patient's electrocardiogram was stabilized continuous sinus and/or pacing rhythm, Adjuvant low-dose colchicine would be beneficial in the treatment and prophylaxis of refractory electrical storm of patients with HFrEF and ICD. It might be replaced instead of proarrhythmic drugs as a novel therapeutic approach.

Keywords: Electrical storm, Colchicine, Pharmacological dechanneling, Misfolded protein.

Introduction

Several reports suggest the occurrence of an electrical storm among 10% to 20% of implantable cardioverter-defibrillator (ICD) recipients.¹⁻⁴ Microtubules are the key components of the cytoskeleton of eukaryotic cells and have an important role as railways in various cellular functions such as intracellular migration and vesicle transport, cell shape maintenance, polarity, cell signaling, and mitosis.⁵ In addition, colchicine binding to beta-tubulin results in curved tubulin dimer and

prevents it from adopting a straight structure. This is due to a steric clash between colchicine and beta-tubulin, which inhibits microtubule assembly and harmful intracellular and intercellular signaling. It cleans the misfolded proteins.⁵⁻¹⁰ Written informed consent was obtained from the patient after the approval of the study protocol by the Local Institutional Committee.

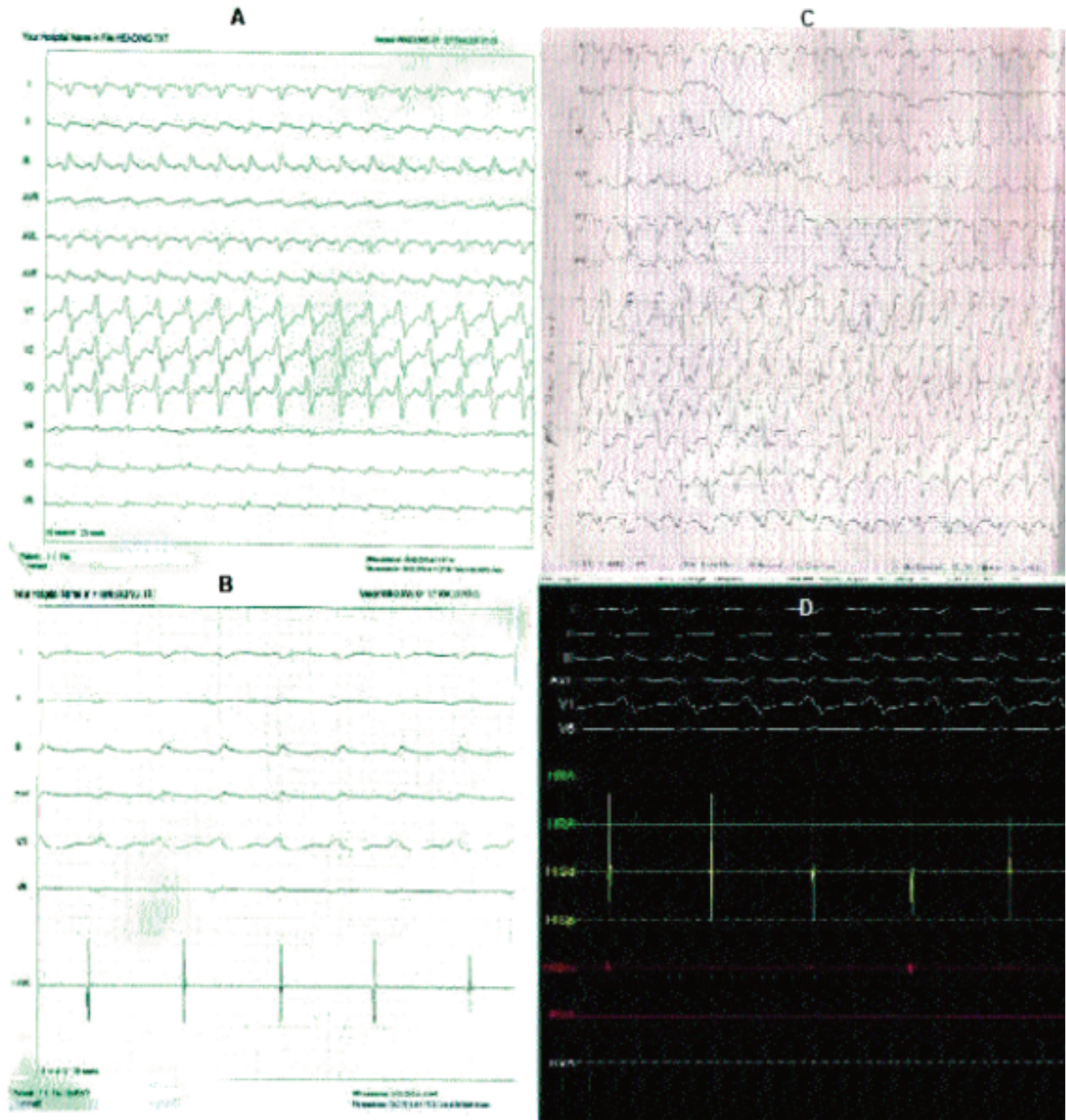
Case Report

A 63-year-old male patient with a history of coronary artery bypass grafting (CABG) following myocardial infarction eight years ago, presented to the Emergency Department of the Istanbul University Cardiology Institute on 27th February 2015. He had a cardioverter-defibrillator (ICD) (VVI-R type) implantation as a primary prevention of sudden cardiac death following recurrent ventricular tachycardia (VT) five years ago. He had increased dyspnoea, oedema, ascites, hepatomegaly, anaemia and was earlier diagnosed as diabetic nephropathy. The presenting ECG revealed ventricular tachycardia with Right Bundle Branch Block pattern in all leads (Figure-1A). Transthoracic Echocardiography (TTE) showed a dilated, hypokinetic left ventricle (LV). Estimated LV ejection fraction (EF) was 28%. Laboratory results were as follows: serum creatinine 2.1 mg/dl, BUN 41, haematocrit 28.9%, platelets 167.000, glucose 90 mg/dl, Na 141 mEq/L, calcium 9.8mg/dl, magnesium 2.04 mg/dl. The haemodynamic status of the patient deteriorated due to VT. The patient was admitted to the coronary intensive care unit. His potassium level was 3.4 mEq/L which was replaced.

At presentation, the patient was receiving conventional heart failure treatment (aspirin 100 mg/day, metoprolol 50mg twice daily, furosemide 40 mg once daily and amiodarone 50mg twice daily). Amiodarone perfusion protocol was started to prevent uncontrolled ventricular tachycardia (electrical storm; ES). MgSO4 1gr perfusion was given during 24 hours due to unresponsiveness, but the ES persisted (Figure 1A-D).

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RBBB, (Right Bundle Branch Block);
 HRA, (High Right Atrium);
 HISd, (Distal His-bundle);
 HISm, (Medial His-bundle);
 HISp, (Proximal His-bundle);
 RVA, (Right Ventricular Apex).

Figure-1: (A,B,C,D) Electrical storms.

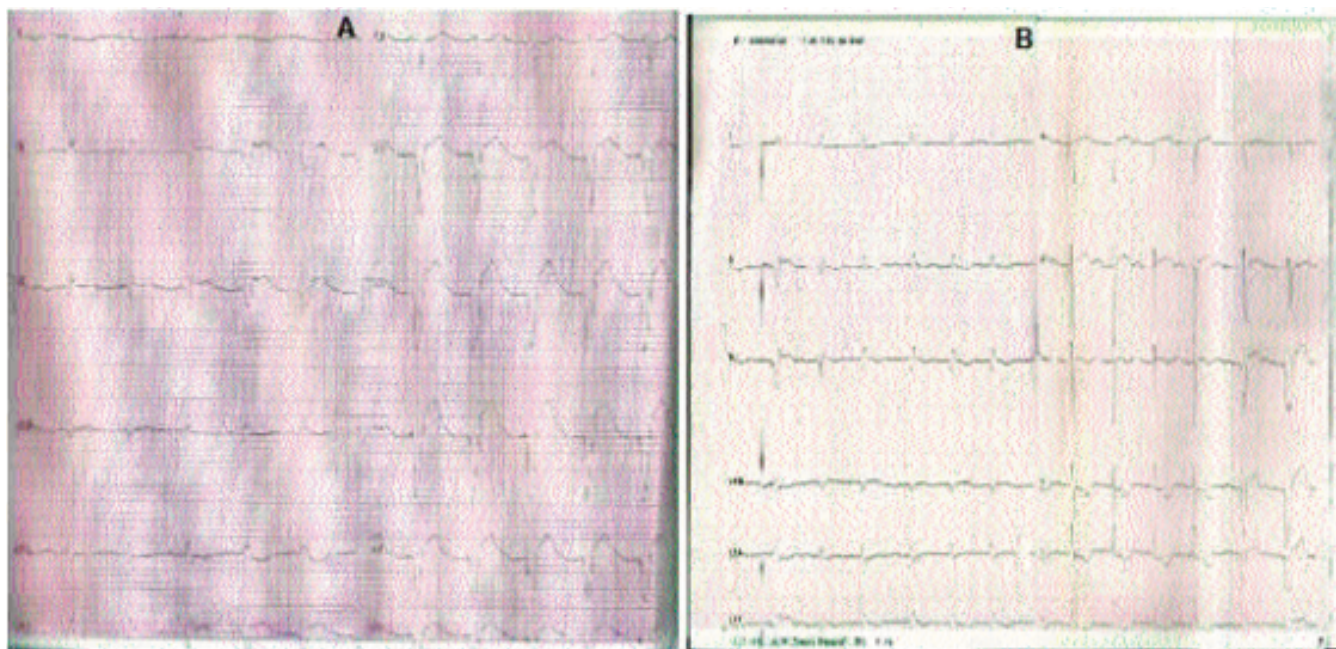


Figure-2: (A, B) After the colchicine treatment, subsequent follow-up of the patient showed continuously sinus and/or pacing rhythm of the ECG recordings for more a year.

An electrophysiologist analyzed all ICD electrograms at the time of the initial ES. An appropriate and/or inappropriate ICD shock was not detected because the VT (ES) was slower than the programmed rate as no shocks were delivered. The electrophysiological investigation showed that ventricular tachycardia originated from the closely spaced dual focus on left ventricular outflow tract. Upon this, anti-tachycardia pacing (ATP) interventions were applied and sinus rhythm returned. A few hours later, VT recurred. In spite of programmed intervention by ATP, VT continued and persisted for days. In his ECG, QT was found as 540 msec. Therefore, oral amiodarone was discontinued. After 80 mg IV bolus of lidocaine, 1mg per minute lidocaine and once again MgSO₄ 1gr was perfused up to twenty-four hours due to QT prolongation. But, VT persisted for days. Based on our previous experience in addition to above medications, the patient was prescribed 0.5 mg adjuvant colchicine once daily to prevent ventricular tachycardia. Seventy-two hours later, ATP was reapplied and cardiac rhythm returned to the sinus rhythm. Subsequent follow-up of the patient showed continuous sinus and/or pacing rhythm of ECG, marked improvements in the patient's clinical status and laboratory findings with a dramatic disappearance of the ES (Figure 2 A, B). The patient rejected three-dimensional electroanatomical mapping and VT ablation intervention. Nowadays, the patient remains in sinus and/or pacing rhythm of ECG and Holter

monitoring, and is clinically well.

Discussion

Several reports suggest the occurrence of an ES among 10% to 20% of ICD recipients. In a vast majority of cases, the recorded arrhythmias were VT's (90%). VF's have been found in only 8% of ES episodes. Reduced LVEF was associated with an increased risk of the electrical storm. Furthermore, the patients treated with Class IA antiarrhythmic drugs were more likely to have an ES. The principal factor in the prevention of electrical instability is correct ICD programming.^{2,3} A patient with ES has to be hospitalized and monitored in an intensive care unit. The most urgent evaluation concerns the haemodynamic stability of the arrhythmias and if they degenerate into acute heart failure, prompt assessment of the complications linked to this (such as pulmonary oedema or acute renal insufficiency). When a trigger can be identified, its correction may reverse the electrical instability of the myocardium. For this reason, thorough clinical and laboratory evaluation is of fundamental importance in order to search for possible proarrhythmic triggers, such as hydro-electrolytic imbalance or the intensification of myocardial ischaemia.¹ If any of these triggers is detected, it must be promptly treated. In some cases, myocardial revascularization is necessary; equally often, however, electrical stabilization is required. The intravenous administration of magnesium and potassium may be

undertaken in patients with QT lengthening or hypokalaemia. With regard to immediate drug therapy, a beneficial effect can be achieved by blocking the sympathetic system through the intravenous administration of beta-blockers combined with sedatives, such as a benzodiazepine. In the absence of contraindications (such as QT lengthening or polymorphic ventricular tachycardia), amiodarone is generally the antiarrhythmic drug of choice and has been validated in numerous clinical trials.¹⁻⁴ If the intravenous combination of amiodarone and beta-blockers proves inefficacious, the addition of lidocaine is a reasonable option.^{1,2} For what concerns the prevention of ES, interesting results have been yielded by some drugs such as azimilide, a class III antiarrhythmic. In cases that are refractory to drug therapy, transcatheter radiofrequency rescue ablation of the arrhythmogenic myocardial substrate can be carried out during ES.¹⁻⁴ We have similarly tried some drugs such as metoprolol, amiodarone, MgSO₄, lidocaine and several anti-tachycardia pacing (ATP) interventions. Also, other antiarrhythmic drugs were not available in Turkey.

Microtubules are the key components of the cytoskeleton of eukaryotic cells and have an important role in various cellular functions such as intracellular migration and transport, cell shape maintenance, polarity, cell signaling, and mitosis.⁵ The real biologic basis by which tubulin inhibition would result in termination of a sustained monomorphic arrhythmia; cannot be fully explained. Low dose colchicine binding to beta-tubulin results in curved tubulin dimer and prevents it from adopting a straight structure, due to a steric clash between colchicine and beta-tubulin. In this way, it would destabilize microtubule assembly, cargo and samurai proteins dynamicity (such as dynein, cofactor dynactin, kinesin, and samurai protein katanin), vesicle transport. Also, it removes scattered and degenerated cellular signal transduction and unifocal block around the arrhythmogenic myocardial substrate (pharmacological scar dechanneling). But, colchicine is a medication with a relatively low therapeutic index, that is why we chose the lower dose. Furthermore, there is no evidence at the bench level or in animal studies to show suppression of ES in animals with colchicine. Therefore, we implemented 0.5mg a low-dose adjuvant colchicine once daily with a view to preventing scar ventricular tachycardia (VT) of the patient in addition to conventional medication to ensure the microtubule destabilization and the pharmacological scar dechanneling. Thus, as previously we reported in one of our patients with Naxos disease,

the enhanced automaticity of ectopic foci and/or reentry circuit around the scar tissue was abolished by cytoskeletal disruption mechanism, induced by tubulin destabilization with low-dose colchicines.⁶ Additionally interesting, colchicine also upregulates other proteins involved in the autophagic clearance of misfolded proteins such as the master regulator Transcription Factor EB (TFEB). For these reasons, colchicine accelerates misfolded proteins are physiologically cleared from the cells by the protein quality control (PQC) system.

The PQC system is composed of two main arms: Firstly the molecular chaperone, mainly represented by the heat shock proteins (HSPs) and secondly the degradative pathways, including the proteasome, the autophagic response and the unfolded protein response (UPR). A specific degradative pathway for a given misfolded protein is selected by defined class of chaperones, with the assistance of co-chaperones. These pathways may determine whether a misfolded protein has to be refolded or degraded. So, the PQC system controls dynamic autophagy. Thus, it occurs with a kind of pharmacologic dechanneling by a clearing of misfolded proteins as autophagic which are completely different and dissimilar from other antiarrhythmic mechanisms. Also, ESs are removed by a low dose colchicine without cellular action potential variation in intact cells.⁶⁻¹⁰

Patients with intractable ventricular arrhythmias such as ES are very difficult to treat. Therefore, we used 0.5 mg adjuvant colchicine once daily to prevent ES of the patient in addition to above medications. This was due to our patient's resistance to conventional pharmacological treatment and multiple ATPs delivered from ICD and deterioration of the overall situation, (Figure-1 A-D). After seventy-two hours, ATP was reapplied and cardiac rhythm returned sinus rhythm. Subsequent follow-up of the patient showed sinus and/or pacing rhythm of ECGs, marked improvements in the patient's clinical status, with a dramatic disappearance of the ESs (Figure-2 A, B).

Conclusions

Adjuvant low-dose colchicine would be beneficial in treatment and prophylaxis of refractory electrical storm of patients with HFrEF and ICD. It might be replaced instead of proarrhythmic drugs as a novel therapeutic approach. Certainly, further studies of colchicine and other microtubule inhibitor derivatives are needed in such patients with ESs due to ICD.

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