*Original article*

# Electrocardiograph abnormalities in patients with active inflammatory bowel disease

K.H. Katsanos, D.K. Christodoulou, K. Pappas, C. Pappas, E.V. Tsianos

## SUMMARY

**AIM OF STUDY: To investigate the prevalence of electrocardiograph (ECG) abnormalities in a cohort of patients with active inflammatory bowel disease (IBD) followed up in a referral center and to compare them with ECG abnormalities in controls. PATIENTS-METHODS: We retrospectively studied surface ECGs from a random selected cohort of IBD patients with active disease and we compared them with ECGs from age and sex matched control individuals. The IBD cohort consisted in total of 34 patients, 22 males (aged 42.3±11.6 years) and 12 females (aged 48.1±13.4 years). Twenty-seven patients were diagnosed with ulcerative colitis (UC) and 7 with Crohn's disease (CD). Disease duration was 10.4±6.2 and 7.8± 4.9 years respectively. Control population consisted of 35 age and sex matched individuals (22 healthy and 13 with viral gastroenteritis). Two cardiologists analyzed ECGs throughout a standard protocol. Differential diagnosis of all abnormal ECGs was based on medical history, concomitant medication and co-morbidity. RESULTS: Twelve out of this 34-IBD patient cohort (35.2%) and 13/35 (37.1%) of control cohort were diagnosed with abnormal ECG's (p=NS). In total 10 UC patients out of 27 (37%) and 2 out of 7 (28.6%) CD patients had evidence of some kind of ECG abnormality. Additionally, seven IBD patients had PR or QRS or QT interval at the upper normal limit. There was no significant difference in the number of ECG abnor-**

**malities between patients and controls but we recorded some qualitative differences between them regarding the type of abnormalities. DISCUSSION: In a cohort of IBD patients with active disease we recorded ECG abnormalities commonly found in healthy individuals and in individuals with viral gastroenteritis. Although we were not able to demonstrate significant differences in overall numbers, we showed qualitative differences regarding types of ECG abnormalities between patients and controls.**

**Key Words:** heart, inflammatory bowel disease, ulcerative colitis, Crohn´s disease, electrocardiograph (ECG).

## INTRODUCTION

A variety of electrocardiograph (ECG) changes have been reported in inflammatory bowel disease (IBD) patients,[1] mainly in those with ulcerative colitis (UC).[2] Interestingly, a study suggested that IBD patients respond to laboratory stressors in the same way as irritable bowel disease patients do.[3]

Electrocardiography changes in endocarditis, myocarditis, pericarditis and acute myocardial infarction in IBD are presented with the same features as in the general population. In UC patients several ECG abnormalities have so far been reported including Wenckebach or[4] complete[5,6] artio-ventricular block, artial fibrillation with supreventicular tachycardia and ST elevations in all leads,[7] ventricular tachyarrhythmia[8] and mesalamine related sinus bradycardia[9] as well as ECG abnormalities during chest pain episodes.[10]

In Crohn's disease (CD) patients under long term parenteral nutrition cardiomegaly and arrhythmia due to selenium deficiency may be present.[11] A study on autoimmune vagal nerve dysfunction[12] suggested that in CD a sympathetic dysfunction predominates; by contrast, autonomic

*1ST Department of Internal Medicine & Hepato-Gastroenterology Unit and *Department of Cardiology, Medical School of Ioannina, Greece*

**Author for correspondence:**

Dr Epameinondas V. Tsianos, Professor of Internal Medicine, 1st Department of Internal Medicine & Hepato-Gastroenterology Unit, Medical School of Ioannina, Leoforos Panepistimiou, 451 10 Ioannina, Greece, tel: ++30-26510-97501, Fax :++30-26510-97016, e-mail: etsianos@cc.uoi.gr

vagal neuropathy predominates in UC. Reported ECG abnormalities in IBD include atrial fibrillation, supraventricular tachycardia, ST elevations, ventricular tachyarrythmia, sinus bradycardia, atrioventricular block, autonomic vagal nerve dysfunction. In addition, any other ECG abnormality associated with endocardium, myocardium and pericardium damage.

The aim of this study was to investigate the prevalence of ECG abnormalities in a cohort of patients with active IBD followed up in our center and to compare them with ECG abnormalities in healthy controls and individuals with viral gastroenteritis.

## Patients-Methods

### Patients

We studied retrospectively surface ECG's from a randomly selected cohort of patients with active IBD followed by our IBD outpatient clinic. This cohort consisted of 34 patients, (22 males, mean age 42.3±11.6 years and 12 females, mean age 48.1±13.4 years). Twenty-seven patients were diagnosed with UC and 7 with CD and disease duration was 10.4±6.2 years and 7.8±4.9 years respectively. Two patients were diagnosed with concomitant diabetes mellitus, one with hyperthyroidism and two with hypertension (Table 1).

No patient underwent colectomy or had ever received total parenteral nutrition. Three patients were admitted to the department of cardiology. All ECG's were obtained during patient's visit to outpatient clinic or patient admission to the department of internal medicine. Files review showed that none of the patients required additional ECG during follow up.

### Controls

Control population consisted of 35 individuals (22 healthy and 13 with viral gastroenteritis) from the same geographical area. There were no significant differences regarding age and sex between patients and controls.

### Study protocol

All individuals underwent ECGs in the same apparatus and in the same examination room.

Two cardiologists examined all ECG's following a standard protocol which included; heart rate (beats/min), rhythm and PR, QRS, QT intervals (measured in msec).

ECG study included three phases. During the first phase no information was given to cardiologists about IBD patient status. All IBD patient abnormal ECG's were included in the second phase and further analyzed with the help of the IBD patient file. Differential diagnosis was made using all available information including medical history and clinical examination. Abnormal ECGs were correlated with IBD activity and disease location in addition to the standard cardiologic differential diagnosis. In such a way we added an IBD-related cardiological diagnosis next to the standard cardiologic diagnosis.

In the third phase of the study we compared all bibliography reports on ECG abnormalities in IBD patients with our ECG findings.

### Statistical analysis

Data was expressed as mean ± SD when normally distributed, otherwise as median with 25 and 75 interquartile percentiles. Comparisons were performed using the chi-square and the exact test when applicable. The 5% level of significance was considered statistically significant. The Excel and the Statistica working packages were used for analysis.

## RESULTS

No significant differences in all ECG parameters were

**Table 1.** Clinical characteristics of IBD patients during study protocol

| All patients (n=34) | UC patients (n=27) | CD patients (n=7) |
|---|---|---|
| Males *(mean age±SD=42.3±11.6)* | 21 | 1 |
| Females *(mean age±SD=48.1±13.4)* | 6 | 6 |
| Disease duration *(years±SD)* | 10.4±6.2 | 7.8±4.9 |
| Colectomy | 0 | 0 |
| Active disease during ECG | All patients | All patients |
| Parenteral nutrition | 0 | 0 |
| Hypertension | 2 | 0 |
| Cardiologic history *(admissions)* | 3 | 0 |
| Thyroid disease *(hyperthyroidism)* | 1 | 0 |
| Diabetes mellitus *(type II)* | 2 | 0 |

noticed between patients and controls. In addition, no significant differences in any of the ECG parameters were noticed between patients and control subgroups namely healthy individuals and individuals with viral gastroenteritis.

Twelve IBD patients (35.2 %) and 13/35 (37.1%) of control cohort were diagnosed with abnormal ECG's (p=NS). All IBD patients with abnormal ECGs were included in the second phase of the study (Table 2). Ten of them (7 males, 3 females) were diagnosed with UC and 2 females were diagnosed with CD. All these patients were on disease relapse (moderate UC and CDAI>250) when their ECG's were performed.

In total 10 out of 27 (37%) UC patients and 2 out of 7 (28.6%) CD patients had evidence of ECG abnormalities. Abnormal ECG parameters included PR and QT abnormal intervals (both in UC and CD patients), abnormal heart rate was noticed in 3 out of 27(11.1%) UC patients. It is also noteworthy that other 7 IBD patients had PR or QRS or QT interval at the upper normal limit. There was no difference between males and females regarding ECG's abnormalities and no correlation of ECG abnormalities with disease location was noticed.

Differential diagnosis was made in all 12 abnormal ECG's initially focusing on current bedside clinical cardiological differential diagnosis. This step was performed after reviewing the patient file about medical history and current therapy. Sinus tachycardia was the most frequent

ECG abnormality noticed in 3 UC patients while other 9 patients showed a large spectum of ECG abnormalities (Table 3).

Finally, we added to the bedside cardiological differential diagnosis the IBD-related ECG diagnosis (Table 4). This phase of the study resulted in a hypothetical IBD-related ECG diagnosis, which was added to the official diagnosis (Table 3, column 3).

All these 12 IBD patients were informed about cardiological diagnosis on their abnormal ECGs. In some of these patients further cardiological investigation and regular follow up was suggested.

## DISCUSSION

In this IBD patient cohort we noticed a large spectrum of ECG abnormalities that, however, did not differ in overall numbers compared to ECG abnormalities found in age and sex matched apparently healthy individuals and in individuals diagnosed with viral gastroentritis.

However the prevalence of types of ECG abnormalities among IBD patient and control population differed, although not reaching statistically significant level, probably due to restricted numbers of cases examined.

This study shows that IBD as a generalized inflammatory condition may lead to a variety of ECG abnormalities which seem to reflect active bowel disease and not a real heart-related problem. Nevertheless, as may happen

**Table 2.** Abnormal ECG parameters in IBD patients and age and sex matched healthy and viral gastroenteritis individuals.

| ECG Parameters | UC patients (n=27) | % | CD patients (n=7) | % | IBD patients (n=34) | % | All controls (n=35) | % | Viral gastroenteritis (n=13) | % | Healthy controls (n=22) | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pacemaker | 0 | *0* | 0 | *0* | **0** | *0* | **0** | *0* | 0 | *0* | 0 | *0* |
| **Heart rate** (b/min)-*abnormal* | 3 | *11.1* | 0 | *0* | **3** | *8.8* | **1** | *2.8* | 1 | *7.7* | 0 | *0* |
| **Rhythm**-*abnormal* | 3 | *11.1* | 0 | *0* | **3** | *8.8* | **2** | *5.7* | 1 | *7.7* | 1 | *4.5* |
| **PR** (msec)-*abnormal*\* | 1 | *3.7* | 1 | *14.3* | **2** | *5.9* | **0** | *0* | 0 | *0* | 0 | *0* |
| **QRS** (msec)-*abnormal*\*\* | 0 | *0* | 0 | *0* | **0** | *0* | **0** | *0* | 0 | *0* | 0 | *0* |
| **QT** (msec)-*abnormal*\*\*\* | 1 | *3.7* | 0 | *0* | **1** | *2.9* | **0** | *0* | 0 | *0* | 0 | *0* |
| **T wave** *abnormal* | 1 | *3.7* | 1 | *14.3* | **2** | *5.9* | **3** | *8.6* | 1 | *7.7* | 2 | *9* |
| **R wave** *abnormal* | 0 | *0* | 0 | *0* | **0** | *0* | **3** | *8.6* | 1 | *7.7* | 2 | *9* |
| **Branch block** (*left/right*) | 0 | *0* | 0 | *0* | **0** | *0* | **3** | *8.6* | 1 | *7.7* | 2 | *9* |
| Ventricular hypertrophy | 1 | *3.7* | 0 | *0* | **1** | *2.9* | **1** | *2.8* | 0 | *0* | 1 | *4.5* |
| All abnormal ECG's | 10 | *37* | 2 | *28.6* | **12** | *35.2* | **13** | *37.1* | 5 | *38.5* | 8 | *36* |

*\*=2 IBD patients (1 with CD, 1 with UC) had PR at the upper normal limit*
*\*\*=3 IBD patients (2 with CD, one with UC) had QRS at the upper normal limit*
*\*\*\*=2 patients with UC had QT at the upper normal limit with respect to the heart rate*

**Table 3.** ECG abnormalities in IBD patients. Probable ECG diagnosis and IBD-related ECG diagnosis

| Patient | Disease | ECG abnormality | Probable diagnosis | IBD-related diagnosis |
|---|---|---|---|---|
| 1 (76ys, F) | UC | Sinus bradycardia | -drugs (digoxin use) | Mesalamine related? |
| 2 (47 ys, F) | UC | Sinus tachycardia | -hyperthyroidism | -stress -hyperactivated sympathetic system? |
| 3 (82ys, F) | UC | Sinus tachycardia | -hyperactivated sympathetic system? | -as patient 2 |
| 4 (42ys, M) | UC | Sinus tachycardia | -hyperactivated sympathetic system? | -as patient 2 |
| 5 (86ys, M) | UC (hypertension) | Ventricular/ atrial ectopics | -ischemia (heavy smoker) | -ischemia |
| 6 (54YS, M) | UC | Early repolarization | -stress -idiopathic | -hyperactivated sympathetic system? -heavy smoker |
| 7 (50ys, M) | UC* | Atrial fibrillation | -ischemia | -heavy smoker |
| 8 (82YS, M) | UC* diabetes | Common atrial ectopics, mean QRS axis>-450 | -Left anterior hemiblock -emphysema, right ventricular hypertrophy | -cor pulmonale |
| 9 (62ys, M) | UC* (hypertension, diabetes) | ST-T wave depression, QT prolongation | -myocardial ischemia | -ischemia -heavy smoker |
| 10 (85ys, M) | UC | Ventricular ectopic beats | -ischemia (heavy smoker) | Same as patient 5 |
| 11 (67ys, F) | CD | Non-specific ST-T wave abnormalities | -hyperactivated sympathetic system | -autonomic vagal nerve dysfunction? |
| 12 (68ys, F) | CD | First degree Atrioventricular block | -drugs -inflammation | -autonomic vagal nerve dysfunction? |

*Patients admitted at the department of cardiology*

in every day's clinical practice, a relapsing IBD may either reveal or further deteriorate a pre-existing cardiovascular problem.

The issue of whether drugs such corticosteroids and mesalazine routinely used in active IBD can induce, on short or long term administration, cardiac complications needs a lot of discussion as studies are lacking. In fact,

**Table 4.** Comparison of reported ECG abnormalities in IBD patients with ECG abnormalities noticed in the present IBD cohort.

| Generally reported ECG abnormalities | This cohort ECG abnormalities |
|---|---|
| Atrial fibrillation | Yes |
| Supraventricular tachycardia | Yes |
| ST elevations | Yes |
| Ventricular tachyarrhythmia | No |
| Sinus bradycardia | Yes |
| Atrioventricular block | Yes |
| Autonomic vagal nerve dysfunction | Yes |
| Pacemaker | No |

it seems that IBD heart-related extraintestinal manifestations are not sufficiently described and documented in prospective studies and are probably underdiagnosed in some silent cases. Moreover, corticosteroids are beneficial in many IBD heart-related complications including pericarditis and myocarditis. In this way corticosteroids successfully treat-even before clinical diagnosis- heart-related complication during IBD, relapse. It is of note that this study included only patients with active IBD needing high doses of steroids in order to achieve remission in some cases.

Cardiac rhythm was sinus in the great majority in IBD patients, with sinus tachycardia being more common than sinus bradycardia. IBD patients with bradycardia not related to drugs such as beta-blockers or digoxin could also be considered to have a mesalazine-related origin until proof of the contrary. Electrophysiologic cardiac conduction system studies could be of help.

Cardiac conduction system defects, although rare, may be present in active IBD as in one CD patient in this study. These defects are not per se indications for preventive

pacemaker implantation unless an overlapping cardiac problem occurs which leads to a more severe type of atrioventricular block.

Ventricular and atrial ectopic beats, not so uncommon in the general population, may also be present in active IBD. It is wishful to exclude in all these patients ischemia, electrolytic disturbances, hemodynamic instability, myocarditis, myocardiopaty, pericarditis, hyperthyroidism, alcohol and drug abuse. This study did not reveal significant differences in ECG abnormalities between UC and CD patients or between males and females. This may be attributed to the non-specific nature of these abnormalities or to the middle aged IBD population used in the study lacking other cardiovascular risk factors. Overall, IBD patients may have cardiac morbidity equal to the general population. As a result of this, any ECG abnormality commonly encountered in the general population may be present in IBD in activity or remission. Nevertheless, experienced IBD clinicians should focus on specific ECG protypes implicating well recognized heart-related IBD complications. These ECG protypes, although non-disease specific, include endocardium, myocardium and pericardium involvement. An increased risk for endocarditis has been suggested for IBD patients and has been reported in less than 30 cases.[13-15] Endocardium involvement is an extremely severe condition in IBD patients which often leads to surgery and always needs hospitalization and intensive treatment.

Myocardium involvement in IBD is a rare but severe complication and is very often associated with pericarditis or pleural effusion in the majority of UC[16-19] patients but rarely in CD patients.[20] The terms myo-pericarditis or perimyocarditis are used to describe these coexistences. A Danish study[21] showed that IBD patients have an increased risk for myocarditis compared with the background population but its incidence is generally low.

Therapeutics in IBD seem also to play an important role; reversible hypertrophic cardiomyopathy complicating prolonged corticotherapy[22] and acute myocarditis[23] and perimyocarditis[24] due to mesalamine use have been reported. Acute myocardial infraction during disease exacerbation in a young patient[25] and a fatal case in an elderly woman[26] are also cases of interest. The interesting possible association of giant cell myocarditis with UC is a topic needing further confirmation.[27-29].

Myocardium involvement in Crohn's disease is mainly due to selenium deficiency during prolonged[30,31] or short term[32] TPN as previously described. Although none of our patients was on TPN, we would like to stress that selenium deficiency is reversible but may result in fatal cardiomyopathy and should always be suspected in TNP patients with palpitation, precordial pain, arrhythmias and cardiomegaly.

It seems that pericardium involvement is the most frequent complication of heart involvement[33-40] in IBD although not found in any of our patients. Pericardium involvement often co-exists with myocarditis or pleural effusions and those cases are described as periomyocarditis or myopericarditis[41] and pleuro-pericarditis respectively.

Pericardium inflammation can be diagnosed in IBD cases as an idiopathic condition[42] (disease-related extraintestinal complication), as a therapy-related side effect or due to pericardio-colonic fistulas[43]. Pericardial tamponade is a rare[44-47] but urgent condition and should always be intensively treated.

Acute infarction was reported during relapse of UC.[25] One patient of this cohort had an episode of acute infarction in the past. In CD patients, in addition to all common conditions and predisposing risk factors, a reversible vasoconstriction diminishing blood flow to the perfused tissues followed by an ischaemia of varying severity was suggested in the pathogenesis of coronary artery involvement in CD.[48] All known cardiovascular risk factors in the general population are also encountered in IBD patients with the exception of abnormally high cholesterol, which seems to be in low-normal or below normal levels in hospitalized or malnourished IBD patients.[49]

Heart amyloidosis has never been reported in UC patients and was not found in any of our patients. Although systemic AA amyloidosis complicating CD has been found in 0.5 to 6% in America and Europe it is seems relatively rare in Japan.[50] Cardiac amyloidosis in IBD results in an extremely poor prognosis; colchicine[51] may be beneficial in treating this type of secondary amyloidosis in which transplantation proved a disappointing solution. Sparkling intraventricular septum appearance in echocardiography and endocardium biopsies positive in Congo red staining are diagnostic hallmarks for this rare but extremely severe complication.

Heart failure may sometimes be the end point of all previously reviewed cases of heart involvement in IBD irrespective of age. Acute heart failure may result from acute myocardial infarction, myocarditis, tamponade and valve destruction during an endocarditis infection. Chronic heart failure is usually caused by valve and myocardium involvement although cases of heart muscle atrophy during TPN[52] and corticosteroid prolonged use[22] has been

reported. Heart related sudden death in UC was reported to be due to myocardial infarction[26] or related to heart muscle atrophy.[29]

Cases of low output cardiac failure in CD patients receiving long-term TPN have been reported.[52,53] Our patient cohort consisted of middle-aged patients but we would like to emphasize that prolonged steroid use resulting in hypertension, high infection risk and heart muscle atrophy has been reported to increase the risk for congestive heart failure in advancing aged CD patients.[54] Intra-operative acute cardiac arrest has also been reported.[55] In a cohort of 1000 CD patients 25 patients (2.6%) had died. Of those 3 died of an acute myocardial infarction.[56]

Anti-TNFa therapy for CD and growth hormone - which in theory might be of help in cases of heart failure in which TNF-a levels were reported to be high and insulin growth factors low- have failed and, surprisingly, result in further disease deterioration.[57,58]

To conclude, in a cohort of IBD patients with active disease we recorded ECG abnormalities commonly found in healthy individuals and in individuals with viral gastroenteritis. Although we were not able to demonstrate significant differences, we showed qualitative differences regarding the type of ECG abnormalities between patients and controls. These differences, although non-disease specific should always be considered important in some selected patient cases. In addition, ECG abnormalities in relapsing IBD patients with previously negative cardiology history should always be suspective of heart involvement as another disease extraintestinal manifestation until the proof of the contrary. Heart-related problems in IBD patients during active disease have to be studied more extensively and therapeutic guidelines need to be addressed.

It still remain to be further clarified in IBD patients whether uncontrolled bowel inflammation represents an additional risk factor for cardiovascular disease, whether active IBD can further complicate previous cardiac problems and finally which is the optimal primary and secondary prevention therapy for IBD patients with cardiac co-morbidity.

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