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## Electrocardiographic changes in hospitalized patients with leptospirosis over a 10-year period

### Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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### Summary

The aim of this study was to investigate the incidence and type of ECG changes in patients with leptospirosis regardless of clinical evidence of cardiac involvement.

A total of 97 patients with serologically confirmed leptospirosis treated at the University Hospital for Infectious Diseases „Dr. Fran Mihaljević“ in Zagreb, Croatia, were included in this retrospective study. A 12-lead resting ECG was routinely performed in the first 2 days after hospital admission. Thorough past and current medical history was obtained, and careful physical examination and laboratory tests were performed.

### Results:

Abnormal ECG findings were found in 56 of 97 (58%) patients. Patients with abnormal ECG had significantly elevated values of bilirubin and alanine aminotransferase, lower values of potassium and lower number of platelets, as well as more frequently recorded abnormal chest x-ray. Non-specific ventricular repolarization disturbances were the most common abnormal ECG finding. Other recorded ECG abnormalities were sinus tachycardia, right branch conduction disturbances, low voltage of the QRS complex in standard limb leads, supraventricular and ventricular extrasystoles, intraventricular conduction disturbances, atrioventricular block first-degree and atrial fibrillation. Myopericarditis was identified in 4 patients. Regardless of ECG changes, the most commonly detected infection was with *Leptospira interrogans* serovar Australis, *Leptospira interrogans* serovar Saxkoebing and *Leptospira kirschneri* serovar Grippotyphosa.

The ECG abnormalities are common at the beginning of disease and are possibly caused by the direct effect of leptospires or are the non-specific result of a febrile infection and metabolic and electrolyte abnormalities. New studies are required for better understanding of the mechanism of ECG alterations in leptospirosis.

### Conclusions:

**leptospirosis • electrocardiography • cardiac defects**

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## BACKGROUND

Leptospirosis a common and dreaded zoonosis of global distribution, caused by infection with pathogenic spirochetes of the genus *Leptospira* [1]. It affects humans in rural and urban settings in temperate and tropical climates [2]. The disease is maintained in nature by chronic renal infection of carrier animals, which excrete the organism in their urine, contaminating the environment. Human infection occurs by direct contact with infected urine or tissues or, more commonly by indirect exposure to the organism in damp soil or water. The major source of infection for humans and animals are mouse-like rodents [3]. Outbreaks may follow periods of excess rainfall and flood [4].

The serovar classification remains useful for epidemiological purposes, as many geographically widespread serovar reservoir associations exist [5]. Interhuman transmission is very rare [6].

According to recent studies on the worldwide incidence of leptospirosis, Croatia is 13<sup>th</sup> in the world and 1<sup>st</sup> in Europe, with an incidence rate of 17.3 cases per million population annually [7]. Leptospirosis is endemic in Croatia, and most commonly occurs in the Sava and Drava river valleys of central and northwestern Croatia and in the Neretva river valley [8–12].

Leptospirosis in Croatia has been systematically monitored and studied for more than 50 years, as a constant object of investigation of infectious disease specialists, epidemiologists, immunologists, veterinarians and foresters [10]. Throughout this time no changes were observed in the incidence rates of leptospirosis in humans and wild animals; however, changes in the incidence rates have been observed among the most likely infectious serovars [5]. Molecular analysis of *Leptospira* spp. isolated from humans demonstrate the diversity of leptospires circulating in Croatia [13]. In Croatia, the highest incidence in the last 10 years has been observed among the following serovars: *Leptospira interrogans* serovar *Australis*, *Leptospira kirschneri* serovar *Grippotyphosa* and *Leptospira interrogans* serovar *Saxkoebing*, as opposed to France, Italy and Germany where *Leptospira interrogans* serovar *Icterohaemorrhagiae* is the most common serovar causing infections in humans [5,13–16].

The severity of leptospiral infections ranges from a sub-clinical illness to 2 clinically recognizable syndromes: a self limited, systemic illness seen in approximately 90% of infections, and a severe potentially fatal illness accompanied by any combination of renal failure, liver failure, pneumonitis with hemorrhagic diathesis and myocarditis [17,18].

Death, occurring in 10–15% of these severe cases, is usually due to pulmonary hemorrhage, renal failure or cardiac failure and arrhythmia secondary to myocarditis [18,19].

The finding of ECG abnormalities in patients with leptospirosis who show clinical evidence of cardiac involvement is well recognized [17,18]. Clinical reports make it clear that pericarditis, endocarditis, myocarditis and arrhythmias occur in leptospirosis [17,18,20]. Cardiac involvement is correlated with the severity of disease [20]. A few systematic studies of latent cardiac involvement in leptospirosis have

been made [21–24]. Experimental studies in animals and autopsies in humans have shown that cardiac involvement in leptospirosis is frequent, even though it may occur without clinical manifestations [25,26].

The aim of this study was to investigate the incidence and type of ECG changes in patients with leptospirosis regardless of clinical evidence of cardiac involvement.

The Ethics Committee of the University Hospital for Infectious Diseases "Dr Fran Mihaljević", Zagreb, Croatia (UHID) approved the study.

## MATERIAL AND METHODS

A total of 97 patients with serologically confirmed leptospirosis treated at the University Hospital for Infectious Diseases "Dr Fran Mihaljević" (UHID) in Zagreb, Croatia, which is the National Reference Centre for Infectious Diseases, were included in this retrospective study from 2000 to 2009. In the investigated period there were 213 hospitalized patients with clinical and epidemiological diagnosis of leptospirosis, which was serologically confirmed in 105 (1 patient with known heart disease was excluded and 7 medical history charts were unavailable). Epidemiological and clinical data including main clinical characteristics and laboratory findings were obtained from hospital charts. The diagnosis was confirmed by microscopic agglutination test (MAT) performed at the Laboratory for Leptospires, Department of Microbiology and Infectious Diseases Clinic, Faculty of Veterinary Medicine, University of Zagreb (2000–2008) and Leptospira Laboratory at the Croatian National Institute of Public Health (2008–2009), with 12 Leptospira serovars: *Leptospira kirschneri* serovar *Grippotyphosa*, *Leptospira interrogans* serovar *Sejroe*, *Leptospira interrogans* serovar *Australis*, *Leptospira interrogans* serovar *Pomona*, *Leptospira interrogans* serovar *Canicola*, *Leptospira interrogans* serovar *Icterohaemorrhagiae*, *Leptospira interrogans* serovar *Tarassovi*, *Leptospira interrogans* serovar *Saxkoebing*, *Leptospira interrogans* serovar *Ballum*, *Leptospira interrogans* serovar *Bataviae*, *Leptospira borgpetersenii* serovar *Poi* and *Leptospira interrogans* serovar *Hardjo*. A cut-off value of >1:500 was used for a significant titre in patients in whom MAT was performed in only 1 serum. In patients with paired serum, those with at least a 4-fold increase in titre were considered positive. In case of co-agglutination, the serovar with the most expressed increase in antibody titre was accepted as pathogenic, and if antibody titers were equal, the finding was accepted as undetermined. Hemorrhagic fever with renal syndrome was excluded.

A 12-lead resting ECG was routinely performed in the first 2 days after hospital admission independent of the clinical manifestations of patients and prior to antibiotic administration. We analyzed all ECGs recorded during the course of disease. ECG recordings were analyzed according to criteria for adults [27]. We considered all nonspecific ST segment and T wave abnormalities to be non-specific ventricular repolarization disturbances. Thorough past and current medical history was obtained, and careful physical examination and laboratory tests were performed.

Exclusion criteria were as follows: prior known alterations in ECG finding, and prior intake of drugs that can influence ECG finding.

**Table 1.** Clinical characteristics, basic laboratory values, and diagnostic findings in 97 patients with leptospirosis.

Characteristics median range	Normal ECG n=41	Abnormal ECG n=56	p
Age (year)	46 (41–52)	48.5 (40.0–59.0)	0.323
Gender: males/females	31/10	42/14	0.945
Duration of symptoms prior admission (days)	4 (4–5.0)	5.0 (4.0–8.0)	0.054
Duration of hospitalization (days)	12 (10.0–16)	14.5 (10.0–20)	0.277
Abnormal chest x-ray	8/41	24/56	0.012
C-reactive protein (mg/L)	104.0 (12.0–184.0)	130.0 (15.5–222.5)	0.220
White blood cells ( $\times 10^9/L$ )	7.5 (6.6–11.4)	10.4 (7.2–12.6)	0.058
Platelets ( $\times 10^9/L$ )	119 (84.0–168.0)	87 (47.0–144)	0.041
Serum creatinine (mmol/L)	108 (96.0–125.0)	134 (96–209)	0.088
AST (IU/L)	51.0 (32.0–86.0)	71.5 (44.5–118.5)	0.044
ALT(IU/L)	61.0 (44.0–120.0)	78.0 (52.0–140.0)	0.122
Bilirubin (mmol/L)	18.2 (15.3–28.9)	25.5 (17.6–43.4)	0.019
Potassium (mmol/L)	4.0 (3.7–4.1)	3.6 (3.4–4.1)	0.006

Values are frequencies or medians with interquartile range.

The variables recorded in each patient included sex, age, duration of disease prior to admission, duration of hospitalization, chest x-ray, white blood cell count, platelets, C-reactive protein, serum creatinine, potassium, alanine aminotransferase, aspartate aminotransferase, bilirubin and urine.

### Statistical analysis

We describe our data with medians and interquartile range for continuous variables, and frequencies for categorical variables. The main clinical characteristics and laboratory findings of patients with normal and abnormal ECG were compared by the chi-square or Wilcoxon rank-sum test. Results were considered significant at  $p<0.05$ . All tests were performed with the SAS software system release 9.1.3 (SAS Institute, Cary, NC).

### RESULTS

Abnormal ECG findings were found in 56 of 97 (58%) patients with serologically confirmed leptospirosis hospitalized at the University Hospital for Infectious Diseases in Zagreb, Croatia from 2000 to 2009. The majority of patients were hospitalized from July to October (68/97 – 70%) and the majority had positive epidemiological anamnesis (90/97 – 93%).

There were no differences in age, sex, duration of symptoms prior to admission or hospital stay between the patients with normal and abnormal ECG (Table 1). The incidence of certain clinical symptoms did not differ with regards to ECG changes (Table 2), nor were there statistical differences in white blood cell count, creatinine, C-reactive protein, and aspartate aminotransferase. Patients with abnormal ECG had significantly elevated values of bilirubin and alanine aminotransferase, lower values of potassium and

lower number of platelets, as well as more frequently recorded abnormal chest x-ray.

ECG was recorded in all patients in the first 2 days after hospitalization when patients were febrile. Non-specific ventricular repolarization disturbances were the most common abnormal ECG finding (Figure 1). Other recorded ECG abnormalities were sinus tachycardia, right branch conduction disturbances, low voltage of the QRS complex in standard limb leads, supraventricular and ventricular extrasystoles, intraventricular conduction disturbances, atrioventricular block first-degree and atrial fibrillation. Myopericarditis was identified in 4 patients on the basis of physician examination (muffled first heart sound), ECG findings (non-specific ST segment and T wave abnormalities, tachycardia, arrhythmias) and echocardiography (Table 3).

In our patients, regardless of ECG changes, the most commonly detected infection was with Leptospira interrogans serovar Australis, Leptospira interrogans serovar Saxkoebing and Leptospira kirschneri serovar Grippotyphosa (Table 4). All patients recovered completely.

### DISCUSSION

Electrocardiographic findings of transient changes found on routine ECG in patients with uncomplicated leptospirosis confirm the predictions of first researchers [19–21] that ECG evidence of cardiac involvement may be found in the absence of physical signs. The first systematic comparative research of ECG findings in a total of 43 patients with leptospirosis and malaria hospitalized from 1960 to 1962 in the British Military Hospital in Malaga and in healthy persons exposed to artificial hyperpyrexia showed that transient ECG abnormalities are similar in patients with

**Table 2.** Clinical symptoms and signs in 97 patients with leptospirosis on admission.

Symptoms	Patients		p
	normal ECG (n=41)	abnormal ECG (n=56)	
Highest recorded temp. °C (median, min, max)	39.8 (39.0–40.6)	39.5 (39.0–40.3)	0.281
General algic syndrome	41/41	56/56	p>0.99
Headache	23/41	35/56	0.525
Vomiting	18/41	23/56	0.780
Diarrhea	18/41	24/56	0.918
Abdominal pain	13/41	19/56	0.818
Jaundice	13/41	26/56	0.144
Conjunctival suffusion	11/41	25/56	0.073
Exanthema	10/41	14/56	0.945

**Table 3.** Electrocardiographic changes in 97 patients with leptospirosis in the first two days after hospital admission.

Characteristics	Patients
Normal finding	41
ST	10
NVRD	13
RBCD	4
ST+NVRD	8
ST+NVRD+LV QRS in SLL	2
ST+RBCD	3
ST+IVCD	1
ST+RBCD+NVRD	1
NVRD+RBCD	1
NVRD+SVES	1
AV block first-degree + NVRD	4
AV block first-degree + RBCD	2
AF	1
AF + RBCD	1
AF + NVRD	3
AF+NVRD+VES	1
<b>Total</b>	<b>97</b>

ST – sinus tachycardia; NVRD – non-specific ventricular repolarization disturbances; RBCD – right bundle branch conduction disturbances; LV QRS in SLL – low voltage of the QRS complexes in standard limb leads; IVCD – intraventricular conduction disturbances; SVES – supraventricular extrasystoles; AV – atrioventricular; VES – ventricular extrasystoles.

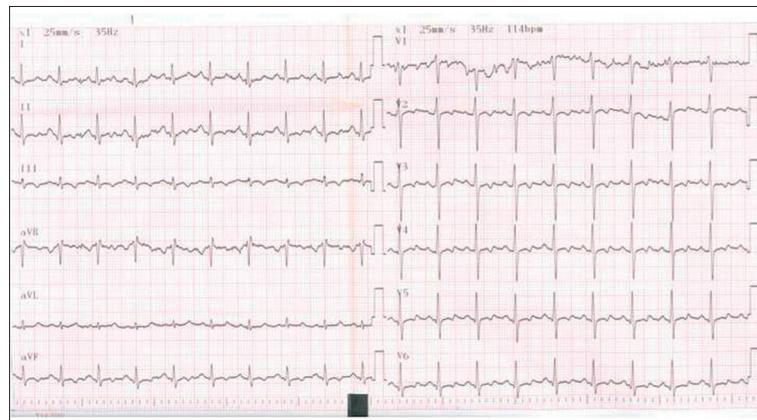
leptospirosis and malaria and are nonspecific results of a febrile infection [24].

Electrocardiographic alterations were detected in 68% of 157 patients hospitalized with leptospirosis in Salvador, Brazil from 1998 to 1999. Atrial fibrillation occurred in 11%, and alterations in ventricular repolarization occurred in 39% of patients. The patients with atrial fibrillation were older, had higher levels of creatinine and aminotransferases, and had evidence of more severe disease. These cardiac manifestations were possibly the result of metabolic and electrolyte abnormalities. The mechanisms determining the ECG alterations were not specifically assessed in the study, nor was the relation between the presence and type of ECG alteration and the prognosis of leptospirosis [28].

The clinical picture of anicteric leptospirosis can closely mimic that of hemorrhagic fever with renal syndrome (HFRS). Both diseases predominantly affect farmers, trappers, veterinarians and military personnel who may have contact with infected animals or their urine. Both diseases are acute febrile diseases most commonly affecting the kidneys, and cause pulmonary and liver disorders as well as ECG abnormalities [29]. Dual infection has been described [30,31]. Although there is no curative therapy for HFRS, antibiotic therapy for leptospirosis is generally believed to be beneficial if initiated early in the course of the disease [32,33]. Therefore, it is important to introduce rapid tests for the detection of both diseases, especially in endemic regions [31].

A total of 1208 patients with serologically confirmed leptospirosis were hospitalized at UHID in the period 1947–1979. In all patients ECG was performed; however, no subclinical transitory ECG abnormalities were recorded [4]. Several published case reports of patients with clinically severe forms of leptospirosis hospitalized in UHID also reported no ECG abnormalities [34–36].

A total of 256 patients with serologically confirmed leptospirosis hospitalized at UHID from 1973 to 1982 were evaluated retrospectively [27]. The purpose of the study was to estimate the incidence of sporadic clinical manifestations in leptospirosis such as electrocardiographic changes. One patient died due to acute myocarditis [38], and 2 had pericarditis. ECG findings of transient changes were seen in 41 (16%) patients. Nonspecific alterations of the ventricular



**Figure 1.** ECG finding: sinus tachycardia (114 min.) with non-specific ventricular repolarization disturbances (inversion of T wave in many leads – II, III, aVF standard limb leads and V1-V6 precordial leads. Artefact in V1 leads).

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**Table 4.** The incidence of leptospira serovars with regards to ECG changes.

<b>Leptospira species/serovar</b>	<b>Patients (n=97)</b>		<b>Total</b>
	<b>ECG normal</b>	<b>ECG abnormal</b>	
Leptospira kirschneri/Grippotyphosa	4	7	11
Leptospira interrogans/Sejroe	2	2	4
Leptospira interrogans/Australis	15	18	33
Leptospira interrogans/Pomona	1	2	3
Leptospira interrogans/Canciola	0	1	1
Leptospira interrogans/Icterohaemorrhagiae	2	4	6
Leptospira interrogans/Tarassovi	0	–	–
Leptospira interrogans/Saxkoebing	9	9	18
Leptospira interrogans/Ballum	0	–	–
Leptospira interrogans/Bataviae	1	0	1
Leptospira borgpetersenii/Poi	2	1	3
Leptospira interrogans/Hardjo	0	1	1
Undetermined, coagglutinins	5	11	16
<b>Total</b>	<b>41</b>	<b>56</b>	<b>97</b>

repolarization were found most often (23 patients), while atrial fibrillation was recorded in 2 patients. In patients with ECG changes, the most frequently observed pathogens were Leptospira interrogans serovar Icterohaemorrhagiae (20), Leptospira kirschneri serovar Grippotyphosa (12) and Leptospira interrogans serovar Sejroe (6) [37].

Among 130 retrospectively analyzed patients with serologically confirmed leptospirosis hospitalized at UHID in the period from 1997 to 2007, 9 (7%) patients developed Weil's disease and were treated at the Intensive Care Unit. The overall case fatality rate was 0.77%. Three patients had acute myopericarditis, and 1 of them developed atrial fibrillation, all with a benign clinical course [39].

We retrospectively analyzed 213 hospitalized patients with clinical and epidemiological diagnosis of leptospirosis which was serologically confirmed in less than half of the patients.

Although in endemic areas, the classic history of fever, myalgia and headache in patients with positive epidemiological anamnesis should raise the possibility of leptospirosis, it should be confirmed by serology. This is supported by research from Iran, where out of a total of 237 patients with clinically and epidemiologically suspected leptospirosis, the diagnosis was confirmed in 74 [40]. Electrocardiograms in our patients were performed in the first 2 days after hospital admission, independent of the clinical manifestations of the patients and prior to antibiotic administration. All patients were febrile at admission and all developed a moderately severe form of disease requiring symptomatic treatment. The following antimicrobials were used: ceftriaxone, co-amoxiclav or doxycycline. A total of 56 (58%) patients had abnormal ECG finding. Myopericarditis was identified in 4 patients. Non-specific ventricular repolarization disturbances were the most frequent ECG disorder. Atrial fibrillation occurred in 6 patients, 1 of whom also had right

bundle branch conduction disturbances, and 4 also had non-specific ventricular repolarization disturbances. In 36 patients control ECGs were performed during hospitalization which proved normal or improved except in 4 patients with atrial fibrillation which did not regress during hospitalization. These patients probably had cardiac predisposition and clinical cardiac manifestation was incited by leptospirosis. In patients with and without ECG changes, the following serovars were most frequently detected: *Leptospira interrogans* serovar Australis, *Leptospira interrogans* serovar Saxkoebing and *Leptospira kirschneri* serovar Grippotyphosa. ECG changes were not related to certain leptospira serovars.

## CONCLUSIONS

ECG alterations and heart disorders indicate that leptospirosis may exhibit tropism for myocardium and contribute directly or indirectly to cardiac disorders during mild, moderate or severe forms of leptospirosis. The presence of transient ECG abnormalities such as sinus tachycardia, non-specific ventricular repolarization disturbances, bundle branch or ventricular conduction disturbances and atrial fibrillation are common at the beginning of disease and possibly are caused by the direct effect of leptospires or febrile infection with a combination of metabolic and electrolyte abnormalities. Further research is required for better understanding of the pathogenesis of leptospiral infections and the mechanism of electrocardiographic alterations in leptospirosis, and to explore the possible relationship between electrocardiographic alterations and the prognosis of leptospirosis.

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## Conflict of interest statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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