Diagnostic Challenges in the Emergency Setting

Doctoral (Ph.D.) thesis

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1 Abbreviations and glossary

ACE-I: angiotensin converting enzyme inhibitors
ACh: acetylcholine
AChEis: acetyl choline esterase inhibitors
AF: atrial fibrillation
ARB: angiotensin II receptor antagonists
CKD: chronic kidney disease
CPR: cardiopulmonary resuscitation
DM: diabetes mellitus
ECG: electrocardiogram
ER: Emergency Room
ESRD: end-stage renal disease
HF: heart failure
HT: hypertension
K suppl: potassium supplementation
nAChRs: nicotinic acetylcholine receptors
OHCA: out-of-hospital cardiac arrest
PLA2: Phospholipase A2
RRT: renal replacement therapy
SfEMG: single-fiber electromyography
V.b.berus: Vipera berus berus
V.b.bosniensis: Vipera berus bosniensis
VF: ventricular fibrillation
VT: ventricular tachycardia
2 Introduction

2.1 The special features of Emergency Care

Healthcare professionals working in the prehospital emergency setting as well as in the Emergency Room (ER) face a multitude of challenges. They are required to diagnose and initiate treatment encompassing a wide range of diseases involving critical thinking and be knowledgeable in various areas of the medical field.

The goal of care in the area of Emergency medicine is to treat illnesses which develop within a short time-frame and which without adequate treatment could lead to negative long-term outcomes for the patients, independent of the patients’ other comorbidities. According to the European Society for Emergency Medicine, time-dependency, allocation of resources and integration into care, epitomize the root principles of Emergency medicine (1). Within the context of providing modern, acute care vulnerable patients are identified and treated based on the severity of their condition in a place where adequate resources for the treatment are readily accessible. Providing optimal, personalized therapy tailored to the patients’ needs is a key feature of this form of medical approach. It also follows, from the underlying principles that time is of the essence when providing Emergency care.

Setting up a timely, accurate diagnosis is essential and failure to do so may have fatal consequences. If a patient is in cardiac arrest, cardiopulmonary resuscitation (CPR) needs to be initiated immediately and the underlying reasons for cardiac arrest concomitantly detected and treated for the optimal short and long-term outcome of the patient (2). Uncovering the cause of a life-threatening medical condition, with limited time available for doing so and often with limited resources and diagnostic tools in the prehospital emergency setting is often a demanding task (3, 4).

On the other hand, even when setting up a diagnosis appears straightforward, physicians at the ER are often faced with the difficulties of interpreting variations in the symptoms caused by the hypothesized illness. In most patients presenting to the ER, common diseases are efficiently recognized and treated based on international guidelines. However, providing care for patients can be challenging when patients with less frequent diseases are admitted to the ER or when evidence regarding the medical condition is lacking.
This thesis includes two important studies, which at first may appear to have little in common. However, the focuses of both studies depict the diverse diagnostic and therapeutic challenges within emergency care. In the first study, the role of the electrocardiogram (ECG) in hyperkalemia is investigated. Then, a unique case of snakebite is reported, where the patient’s symptoms and medical findings are described.

The choice of topics unequivocally shows the difficulties inherent in Emergency Care. Common and/or potentially life-threatening medical conditions, such as hyperkalemia in our study, must be recognized and treated as soon as possible, and evidence-based step-by-step protocols are available for the treatment of this condition. The use of ECG as a simple tool for the prompt diagnosis of this electrolyte disorder appears attractive however, medical professionals must be aware of its limitations. By gathering data regarding the role of the ECG in setting up a diagnosis in hyperkalemic and normokalemic patients, we aimed to help the work of health care professionals in the prehospital and hospital emergency setting. This is particularly important in cases when a patient develops life-threatening arrhythmia and laboratory test results are not immediately available. The physician is then confronted with the difficulty of deciding whether to treat a suspected hyperkalemia, even if he or she is fully aware of the pertaining guidelines.

Although guidelines provide considerable assistance in the treatment of common diseases and - in some instances- in rare medical conditions as well, adequate information regarding the treatment of rare medical conditions, such as snake envenoming by certain species may be lacking or may not be valid in some individual cases. In such instances, the emergency physician is required to follow protocols for the specific treatment of the snake envenoming but the ability to provide personalized care based on the unfolding symptomatology is also essential for achieving the most optimal results. The significance of case reports within all medical fields is unquestionable because they describe the special aspects and treatment options of conditions, where guidelines cannot be followed for one or more of the reasons described above. Therefore, we found it important to describe the rare case of a snake envenoming by the *Vipera berus bosniensis*, thereby adding valuable information to the limited data currently available in the literature.

Thus, the thesis handles one common and one rare medical condition, such as hyperkalemia and snake envenoming, which are excellent reflections of the variety of challenges health care professionals face in Emergency Care.
2.2 Importance of hyperkalemia in emergency care

Over half of all cardiovascular deaths are due to sudden death, with the cause being sudden cardiac arrest and taking place as out-of-hospital cardiac arrest (OHCA) (5). Sudden cardiac arrest has a multifactorial background and is usually preceded by ventricular tachycardia (VT) or (VF) (6). Mortality from sudden cardiac arrest affects over 400 000 people in Europe each year (7). Risk factors of cardiac arrest include heart disease, such as coronary heart disease and congestive heart failure, diabetes mellitus, inherited factors and electrolyte imbalances (5).

According to the European Resuscitation Council, independent of the underlying reason for cardiac arrest, the essential primary interventions include early recognition of the condition, calling for help, early defibrillation, high-quality cardiopulmonary resuscitation and the treatment of reversible causes (2). In periarrest situations and during resuscitation it is essential to rule out reversible causes, such as the ‘4 Hs and 4 Ts’, indicating Hypoxia, Hypo/Hyperkalemia and other electrolyte disorders, Hypo/Hyperthermia, Hypovolemia, and Tension pneumothorax, Tamponade (cardiac), Thrombosis and Toxins (poisoning) (2).

From these, hyperkalemia, a relatively common condition, may lead to fatal cardiac arrhythmias. The incidence of hyperkalemia in hospitalized patients is relatively high and varies between 1.1 and 10 % (8-10). Therefore, electrolyte disturbances should be suspected in patients at risk, with comorbidities, such as diabetes mellitus and cardiac or renal failure. Based on the 2015 guidelines of European Resuscitation Council, electrolyte disturbances, such as hypo- and hyperkalemia should be corrected preferably before cardiac arrest happens (2). Although, portable devices are readily accessible in prehospital care to measure temperature, oxygen saturation and blood glucose levels, the diagnosis of hyperkalemia in prehospital settings is currently not possible. Since alterations in the ECG-s of patients with hyperkalemia have been documented in a number of investigations, ECG-s have been suggested to facilitate a non-invasive approach to diagnosing hyperkalemia (11).
2.3 Symptoms and causes of hyperkalemia

The complaints, symptoms and physical findings of hyperkalemia are non-specific. They may include symptoms such as abdominal pain, nausea, vomiting, weakness, muscle twitching, paraesthesia, paralysis, dysarthria, and dysphagia (12, 13). Physical findings of arrhythmia, hypotension and respiratory or cardiac arrest may be observed in patients with hyperkalemia (12, 13).

The causes of hyperkalemia are multifactorial and encompass a wide range of medical conditions. The main reasons underlying hyperkalemia include, renal failure (acute and chronic kidney disease), drugs (angiotensin converting enzyme inhibitors (ACE-I), angiotensin II receptor antagonists (ARB), beta-blockers, potassium-sparing diuretics and non-steroidal anti-inflammatory drugs), metabolic acidosis, endocrine disorders (for e.g. Addison’s disease), inappropriate diet (particularly in patients with chronic kidney disease), conditions with tissue breakdown (e.g. tumor lysis, rhabdomyolysis, haemolysis) and spurious (pseudo-hyperkalemia) (2, 14). Medications often associated with hyperkalemia are shown in Table 1.

Medications associated with hyperkalemia

The following medications contribute to the development of hyperkalemia:

- Heparin
- Calcineurin inhibitors
- Angiotensin-converting enzyme inhibitors
- Angiotensin II receptor blockers
- Nonsteroidal anti-inflammatory drugs
- Potassium-sparing diuretics
- Trimethoprim
- Pentamidine

Table 1 Adapted from: Runner’s new diet, his collapse, and his ECG: when a rapid ECG diagnosis can save the day by Ringer M, Pulfrey S, Can Fam Physician. 2014 Apr;60(4):340-4.
2.4 ECG alterations caused by hyperkalemia

The concentration of potassium in the serum is tightly regulated between 3.5 and 5.5 mmol/l. Potassium levels are considered elevated above 5.5 mmol/l (15). However, there is no exact definition of hyperkalemia, because the occurrence of symptoms associated with hyperkalemia gradually increases with the elevation of serum potassium levels. Severe hyperkalemia is generally defined as a serum potassium level above 6.5 mmol/l -7 mmol/l (15, 16).

The concentration gradient of potassium existing between intracellular and extracellular fluid compartments enhances the excitability of nerve and muscle cells, including those of the heart. The pH of the serum affects potassium levels. In alkalaemia potassium flows from the vascular to the cellular space, while in acidaemia the potassium moves in the opposite direction (2). Elevated serum potassium levels induce a lowering of the resting membrane potential, slowing of the velocity of phase 0 of the action potential, which in turn leads to the slowing of conduction (17). Meanwhile, the transmembrane potassium permeability increases, which raises the action potential’s phase 3 velocity, thus decreasing the length of the action potential (17). The characteristic ECG changes of hyperkalemia reflect these electrophysiological effects (18). Patients with end-stage renal disease (ESRD) have been thought to develop a tolerance for hyperkalemia, which results in that the commonly observed cardiac and neuromuscular sequence of symptoms present in patients with normal renal function are not visible in ESRD patients (19, 20).

As the level of serum potassium increases, typical ECG alterations appear in a characteristic sequence (16). Mildly elevated potassium levels (5.2-5.9 mmol/l) may cause tall T waves or peaked/tented T waves (16). These are often described as symmetrically narrow, though the deflection is often wide and of large amplitude (16). Although tall, “hyperacute” T-waves are a sign of acute myocardial ischemia and can be mistaken for the peaked T-waves of hyperkalemia, peaked hyperkalemic T-waves tend to be narrow with a prominent or sharp apex (21). Furthermore, pseudonormalization of inverted T waves associated with left ventricular hypertrophy can occur (22). The acceleration of the terminal phase of repolarization is often responsible for these T wave alterations and can best be detected in the precordial leads (16). As the level of serum potassium rises further, cardiac conduction between heart muscle cells is repressed. The cellular action potential is decreased through the inactivation of the sodium channel (16). Moderately elevated potassium levels (6.0-7.0
mmol/l) typically result in PR interval prolongation, decreased P wave amplitude, disappearance of the P wave, widening of the QRS complex or conduction blocks with escape beats and the loss of the P wave (16). Since atrial tissue is more sensitive to potassium level changes P wave flattening and PR interval prolongation are generally visible prior to the prolongation of the QRS interval. The QRS complex in hyperkalemia may liken the appearance of a right or left bundle branch block alteration, except the conduction delay is seen throughout the QRS complex, and not just in the initial or terminal parts of the complex, as is visible in bundle branch block (23). Bypass tracts are also more sensitive to delayed conduction due to increasing potassium levels, which can lead to the normalization of the ECG in patients with Wolff-Parkinson-White syndrome (16). In severe hyperkalemia (>7.0 mmol/l) a markedly prolonged and wide QRS can fuse with the T-wave, causing a “sine-wave” appearance on the ECG, which can induce a fatal event such as ventricular fibrillation and asystole (16). As described in previous reports, however, metabolic changes, such as hypernatraemia or hypercalcaemia can diminish the transmembrane effects of hyperkalemia, so as to make the ECG changes suggestive of hyperkalemia less apparent (24).

2.5 Treatment of hyperkalemia in adults

The main focus of the treatment of life-threatening hyperkalemia is to block the effects of potassium on myocyte transmembrane potential and cardiac conduction and to decrease the level of extracellular potassium (16). If the patient with hyperkalemia is not in cardiac arrest, the patient should be assessed according to the ABCDE approach, intravenous access obtained, serum potassium checked and a 12-lead ECG recorded. Cardiac rhythm should be monitored in patients with severe hyperkalemia (2). Treatment should be initiated according to the hyperkalemia emergency treatment algorithm, as shown in Figure 1.

According to the European Resuscitation Council Guidelines for Resuscitation 2015 the treatment of hyperkalaemia, depends on the severity of hyperkalemia, and should be initiated according to the following protocol (2):

Mild elevation (5.5–5.9 mmol L⁻¹). (2):

• Address cause of hyperkalaemia to correct and avoid further rise in serum potassium (e.g. drugs, diet).
• If treatment is indicated, remove potassium from the body: potassium exchange resins—calcium resinonium 15–30 g, or sodium polystyrene sulfonate (Kayexalate) 15–30 g, given either orally or by retention enema/PR (per rectum) (onset in >4 h).

**Moderate elevation (6.0–6.4 mmol L\(^{-1}\)) without ECG changes.** (2):

• Shift potassium intracellularly with glucose/insulin: 10 units short-acting insulin and 25 g glucose IV over 15–30 min (onset in 15–30 min; maximal effect at 30–60 min; duration of action 4–6 h; monitor blood glucose).

• Remove potassium from the body (see above; consider dialysis guided by clinical setting)

**Severe elevation (≥6.5 mmol L\(^{-1}\)) without ECG changes.** (2):

• Seek expert help.

• Give glucose/insulin (see above).

• Give salbutamol 10–20 mg nebulised (onset in 15–30 min; duration of action 4–6 h).

• Remove potassium from the body (consider dialysis).

**Severe elevation (≥6.5 mmol L\(^{-1}\)) with toxic ECG changes.** (2):

• Seek expert help.

• Protect the heart with calcium chloride: 10 mL 10% calcium chloride IV over 2–5 min to antagonise the toxic effects of hyperkalaemia at the myocardial cell membrane. This protects the heart by reducing the risk of VF/pVT but does not lower serum potassium (onset in 1–3 min).

• Use shifting agents (glucose/insulin and salbutamol).

• Remove potassium from the body (consider dialysis at outset or if refractory to medical treatment)
**Modifications to cardiopulmonary resuscitation. (2):**

The following modifications to standard ALS guidelines are recommended in the presence of severe hyperkalaemia:

- Confirm hyperkalaemia using a blood gas analyser if available.

- Protect the heart: give 10 mL calcium chloride 10% IV by rapid bolus injection.

- Shift potassium into cells: Give glucose/insulin: 10 units shortacting insulin and 25 g glucose IV by rapid injection. Monitor blood glucose.

- Give sodium bicarbonate: 50 mmol IV by rapid injection (if severe acidosis or renal failure).

- Remove potassium from body: Consider dialysis for hyperkalaemic cardiac arrest resistant to medical treatment.

Consider use of a mechanical chest compression device if prolonged CPR is needed.
Figure 1: Emergency treatment of hyperkalemia. (PR: per rectum; VT: ventricular tachycardia)

Reproduced with permission from the Renal Association and Resuscitation Council (UK).
2.6 Aims of the study regarding ECG alterations in hyperkalemia

Despite ECG manifestations considered typical for hyperkalemia, the clinical diagnosis of hyperkalemia remains difficult as the electrophysiological disturbances listed above are not pathognomonic of potassium disorders nor do they appear in each patient with hyperkalemia (25). According to earlier studies, the prevalence of ECG alterations in hyperkalemia was as low as 14-59% of the cases (18, 25, 26). Reports about severe cases of hyperkalemia with none or minimal ECG alterations have also been published (18, 27).

A number of investigations have studied the correlation between elevated potassium levels and changes in the ECG (25, 26, 28). To our knowledge, however, no investigation has been conducted regarding the presence of ECG manifestations suggestive of hyperkalemia in patients with normal potassium levels.

The goal of our study was to compare the prevalence of ECG alterations suggestive of hyperkalemia in normokalemic and hyperkalemic patients. It was also our objective to examine the frequency of certain ECG alterations possibly associated with elevated potassium levels. By investigating the frequency of ECG changes in both groups of patients we aimed to elucidate whether these ECG alterations may facilitate recognition of hyperkalemia in the prehospital setting.

2.7 The medical relevance of snake envenomation

Throughout the world, hundreds of thousands of patients are affected by snakebite envenomation annually. Although snakebites are not as prevalent in Europe as in the subtropical and tropical regions of the world, certain snake subspecies of the genus Vipera account for serious envenomation and may lead to long-term consequences or even death in some patients (29). In Europe there are three species of venomous snakes categorized as medically important: Vipera berus, Vipera aspis, and Vipera ammodytes. V. berus is the most widespread species, present both in North-east and Central Europe. Clinically, Vipera berus berus and Vipera aspis aspis envenomations mostly cause local symptoms, but have been associated with causing systemic symptoms as well (hypotension, gastrointestinal and coagulation disorders, neurotoxicity) in cases of severe envenomation (30, 31)
2.8 The common adder (*Vipera berus*)

In Hungary, the common adder is the sole native venomous snake species of medical relevance. The lowland adder populations of Somogy County in South-Western Hungary are currently recognized as the Balkan or Bosnian adder, *V. b. bosniensis* (32). However, differences in the appearance between the nominate subspecies (*V. b. berus*) and the Bosnian subspecies, are not evident for laymen. Melanistic and very dark specimens can frequently be observed in these lowland adder populations (32, 33) (*Figure 2 A, B, C*).

*Figure 2. (A) A darkish coloured adult male specimen of *V. b. bosniensis* from Darvaspuszta. (B): A full melanistic *V. b. bosniensis* from Kaszo. (C): The culprit: a sub-adult melanistic specimen that caused the incident in Kaszo. (Photographs were taken by: (A) Tamas Malina; (B) Gergely Babocsay; (C) the patient.)*

The first record of the occurrence of the adder in Somogy County dates back to the end of the 1920s. Specimens were collected in Kaszó by Dudich (34). Later Marián (35) thoroughly studied the geographical distribution range of *V. berus* populations in Somogy County during his field works. The earliest recorded snakebite accident caused by this taxon in this county was reported by Marián (33); the envenomed patient was transported to the Hospital of
Kaposvár in July 1951. In another historical case, a local forester was bitten by an adder near Homokszentgyörgy and the patient was admitted condition to the medical institute mentioned above in a critical, life-threatening condition (36).

In Central Europe, the common adder (Vipera berus) is ranked into category 2 based on its medical importance (37). According to the definition of WHO (2016) (37), the species belonging to this category are “highly venomous snakes capable of causing morbidity, disability or death, but for which exact epidemiological or clinical data may be lacking and/or are less frequently implicated (due to their activity cycles, behaviour, habitat preferences or occurrence in areas remote to large human populations)”.

The common adder is considered a relatively small snake with an average length of 50-70 cm. The thick-set body of the snake ends in a short tail, with a dark zig-zag shaped streak a characteristical feature running across the length of the snake’s back. V. b. berus is characterised by gender dichromatism, while V.b. bosniensis by its somewhat shorter length and lack of dichromatism. The snakes are generally brown in color, with a varying ratio of melanistic individuals. There are a relatively high number of dark, melanistic individuals in the South-Hungarian population of V.b. bosniensis. (38)

2.9 Envenoming by the common adder (Vipera berus). Symptoms.

Vipera berus envenomings are well documented in the medical and toxicology literature (39, 40). The purpose of snake venom is to enable the subduing and digesting of the prey. Venoms are made up of biologically active proteins: of synergistically functioning toxins and enzymes. There is a variation between the venom composition of individual snakes within the same species, which is heavily dependent on the snake population’s geographic distribution (41). Certain signs and symptoms of envenomings are suggestive of this potential intraspecies venom variation – between different populations and at the intra-population level as well. The diversity of snake venom within a given species has previously been described in a number of reports, among members of the genus Vipera as well (41-43).

In a recent study, venom samples from several individual European adders (Vipera berus berus) within a defined population in Eastern Hungary were examined (44). Individual variations of venom components were identified and protease activity measured with
zymography (44). This showed that the protease activity constituting different venom patterns of the individuals were related to the adders’ gender and age. The activity of the key component of venom neurotoxicity, Phospholipase A<sub>2</sub> (PLA2) activity of venoms was shown to be similar but not identical. The extracted venom samples differed in their neuromuscular paralysing effect on chick biventer cervicis nerve-muscle preparations (44). The report clearly demonstrated the individual venom variation among V. b. berus living in particular area of Eastern Hungary. (44) Table 2 shows the list of case reports about neurotoxic envenoming by V. b. berus envenomings in the Carpathian basin.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of incident</th>
<th>Place of incident</th>
<th>Age of patient</th>
<th>Sex of patient</th>
<th>recorded carnival nerve disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blatt (1923)</td>
<td>1922</td>
<td>Transylvania</td>
<td>40 years</td>
<td>F</td>
<td>accommodation trouble, ophtalmoplegia, bilateral ptosis</td>
</tr>
<tr>
<td>Malina et al. (2008)*</td>
<td>1878</td>
<td>Western Transylvania</td>
<td>24 years</td>
<td>M</td>
<td>bilateral ptosis, blindness</td>
</tr>
<tr>
<td>Malina et al. (2008)**</td>
<td>1895</td>
<td>Western Transylvania</td>
<td>43 years</td>
<td>F</td>
<td>ophtalmoplegia</td>
</tr>
<tr>
<td>Malina et al. (2008)</td>
<td>2007</td>
<td>Eastern Hungary</td>
<td>27 years</td>
<td>M</td>
<td>diplopia, ophtalmplegia</td>
</tr>
<tr>
<td>Gafencu et al. (2012)</td>
<td>not mentioned</td>
<td>South-Western Romania</td>
<td>14 years</td>
<td>F</td>
<td>blurred vision, bilateral ptosis, dysphagia</td>
</tr>
<tr>
<td>Malina et al. (2013)</td>
<td>2012</td>
<td>Eastern Hungary</td>
<td>12 years</td>
<td>F</td>
<td>bilateral but partial ptosis, gaze paresis, diplopia</td>
</tr>
<tr>
<td>Strugariu and Strugariu (2014)</td>
<td>2003-2011</td>
<td>North-Eastern Romania</td>
<td>9 years</td>
<td>F</td>
<td>bilateral ptosis</td>
</tr>
</tbody>
</table>

Table 2: List of case reports about neurotoxic envenoming by V. b. berus envenomings in the Carpathian basin.

Adapted from Individual variability of venom from the European adder (Vipera berus berus) from one locality in Eastern Hungary by Malina T et al., Toxicon. 2017 Sep 1;135:59-70.
Therefore, it is not surprising that occasionally relatively uncommon and/or atypical signs and symptoms develop in envenomed patients bitten by *V. berus* in different regions. The medical importance of this variability in venom composition is underlined by the observation that following snakebite patients may produce a wide range and severity of symptoms and therefore, need to be appropriately treated.

The bite of the common adder usually affects the limbs, with an equal number of bites having been reported on the upper as on the lower extremities (45). Two penetrating wounds are visible 3-10mm-s apart, indicating the imprint caused by the fangs. The ensuing edema of the area may hide these marks (38).

The typical symptoms of common adder envenomation initially include local symptoms. Following the needle-like sharp pain inflicted by the bite itself, envenomation causes a burning, then throbbing pain within minutes to half an hour of the bite. Local swelling and erythema generally ensue and the edema may reach its peak between 48-72 hours and gradually resolve within 2 weeks. In many but not all cases, the venom contains hemorrhagic toxins, which cause hematomas, haemorrhages and petechias (39, 46).

Systemic symptoms may accompany local symptoms. Nausea, dizziness, tachycardia, vomiting, abdominal cramps, diarrhoea and weakness are almost always present (39) (46). The cardiovascular system of the patient is generally affected, causing dangerous medical conditions, such as hypotension and arrhythmias and occasionally high blood pressure levels as well. Regional lymphadenopathy can also occur. Mostly the venom of the individuals populating the South-western region of the country can affect the peripheral nervous system, primarily the cranial nerves, thus often inducing diplopia, ptosis, dysarthria and/or impaired vision (39, 46).

2.10 Pathophysiology underlying venom-induced neurotoxicity

Reports of neurological manifestations in patients bitten by *V. b. bosniensis* have been published in the last couple of years (Persson, 2015) thereby expanding the knowledge on the clinical presentation of envenomings. Earlier (47, 48), already emphasized that the venom of the Serbian adders living in the Sava Valley can induce peripheral neurotoxicity in humans. These lowland adder populations are currently also recognized as *V. b. bosniensis* (49). Oculomotor nerve palsy, as a characteristic sign in patients bitten by specimens of adder
populations in Somogy County, was initially mentioned by Fejérváry (50) without a detailed description, though.

The pathophysiological explanation for peripheral neuromuscular weakness after snakebite is caused by the venom’s effect to disrupt the neuromuscular junction transmission (51). Neurotoxins produce their effect at the site of the neuromuscular junctions pre- or post-synaptically. As a response to the incoming nerve action potential causing the influx of calcium ions the motor nerve axon terminal synthesises and releases the neurotransmitter acetylcholine (ACh) (52-54). This process is the result of an intracellular signalling cascade involving SNARE proteins (52-54). Nicotinic acetylcholine receptors (nAChRs) enable the release of ACh. Disturbances of neuromuscular transmission can occur at the presynaptic level, affecting calcium and potassium channels, SNARE proteins or nAChRs (51).

As Ach is released into the synaptic cleft, it is degraded by acetyl cholinesterase, in order to terminate its action.

Post-synaptically, ACh binds to muscle nAChRs, which are ligand-gated ion channels. End-plate potential is effected through the influx of sodium and calcium ions and efflux of potassium (52-54). If adequate Ach is released, muscle contraction occurs. Post-synaptic neuromuscular block can be depolarising or non-depolarising. Depolarising neuromuscular blocking agents, such as suxamethonium bind irreversibly to the post-synaptic muscle nAChRs, while non-depolarising blocking agents such as curare competitively inhibit Ach binding to nAChRs (52-54). It follows that these latter neuromuscular blocking agents can be antagonized by acetyl choline esterase inhibitors (AChEis), like neostigmine. It has also been shown that non-depolarising agents can produce pre-synaptic effects as well, which is neurophysiologically demonstrated by the combination of reduction in twitch amplitude (indicating post-synaptic blockade) and fade of the twitch height responses on repetitive stimulation (due to pre-synaptic blockade) (52-54).

Snake neurotoxins can have pre- or post-synaptic activity. Pre-synaptic snake toxins have potent phospholipase A2 (PLA2) activity, while post-synaptic snake toxins include alpha-bungarotoxin and candoxin to name a few (51).

Figure 3 shows the sites of action of snake neurotoxins and other substances on the neuromuscular junction. (51)
Sites of action of snake neurotoxins and other substances on the neuromuscular junction.

Schematic representation of the neuromuscular junction showing different sites of action of snake neurotoxins, other toxins, and pharmacological substances, and sites of involvement in disease states (examples indicated where relevant).

1. **Synaptic vesicular proteins:**
   - **Snake toxins:** beta-bungarotoxin (*Bungarus* spp.), taipoxin (*O. scutellatus*);
   - **Other toxins:** botulinum toxin, tetanus neurotoxin.

2. **Voltage-gated calcium channel:**
   - **Snake toxins:** calciseptine (*Dendroaspis* spp.), beta-bungarotoxin (*Bungarus* spp.);
   - **Other toxins:** omega-conotoxin (marine snail, *Conus* spp.);
   - **Disease states:** Lambert-Eaton myasthenic syndrome.

3. **Pre-synaptic membrane:**
   - **Snake toxins:** phospholipase A2 toxins.

4. **Pre-synaptic ACh receptor:**
   - **Snake toxins:** candoxin (*Bungarus candidus*);
   - **Other toxins:** curare;
   - **Pharmacological substances:** non-depolarising blocking drugs (atracurium).

5. **Voltage-gated potassium channels:**
   - **Snake toxins:** dendrotoxins (*Dendroaspis* spp.);
   - **Disease states:** neuromyotonia, Isaacs’ syndrome;
   - **Pharmacological substances:** magnesium sulphate, aminoglycosides.

6. **Acetylcholine:**
   - **Lysis by exogenous acetylcholinesterase in snake venom:** cobra venom (*Naja* spp.).

7. **Acetylcholinesterase:**
   - **Inhibitors of endogenous AChE in snake venom:** fasciculins (*Dendroaspis* spp.).

8. **Post-synaptic ACh receptors:**
   - **Snake toxins:** alpha-bungarotoxin (*Bungarus* spp.), candoxin (*B. candidus*), azemiopsin (*A. feae*), waglerin († *T. wagleri*);
   - **Other toxins:** alpha-conotoxin (marine snail, *Conus* spp.);
   - **Disease states:** myasthenia gravis;
   - **Pharmacological substances:** depolarising blocking agents (e.g., succinylcholine), non-depolarising blocking drugs (e.g., atracurium).

9. **Voltage-gated sodium channels:**
   - **Snake toxins:** crotamine (*Crotalus* spp.);
   - **Other toxins:** pompilidotoxin (wasps), delta-conotoxin (*Conus* spp.), tetrodotoxin (pufferfish).

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**Figure 3:** Sites of action of snake neurotoxins and other substances on the neuromuscular junction

Adapted from *Neurotoxicity in snakebite—limits of our knowledge.* by Ranawaka UK et al. *Negl Trop Dis.* 2013 Oct 10;7(10):e2302
2.11 The aims of the case report on V. b. bosniensis envenomation

The aim of this publication is to expand the knowledge about the envenoming due to *V. b. bosniensis* bite by describing a case which resulted in minimal local symptoms but severe neurological manifestations and other, persistent systemic venom effects in an adult patient. This is the first photographically-documented neurotoxic case that occurred in South-Western Hungary, in the northernmost geographical distribution range of this taxon.
2.12 The goals of my study

Taken together, the goals of my studies were to determine the following:

Regarding the study on ECG alterations in normokalemic vs hyperkalaemic patients:

1. Are there any differences between the baseline characteristics (age, comorbidities, medication, mortality rate) of normokalemic and hyperkalemic patients admitted to the Emergency Department?

2. What is the frequency of ECG alterations suggestive of hyperkalemia in patients with normokalemia, moderate hyperkalemia and severe hyperkalemia?

3. What kind of ECG alterations indicative of hyperkalemia were more common in patients with moderate or severe hyperkalemia than in patients with normokalemia?

4. Are there any differences between the frequency of ECG alterations possibly associated with hyperkalemia, such as atrial fibrillation, short or long QTc and ST depression, in normokalemic versus hyperkalemic patients?

5. Is there a correlation between the occurrence of certain ECG alterations and the severity of hyperkalemia?

6. Is the ECG a suitable tool in the diagnosis of hyperkalemia in the prehospital, emergency setting?

Should therapeutic decisions and interventions be made based on the ECG signs of hyperkalemia alone?
Regarding the case report on V.b. bosniensis envenoming:

7. Which characteristic and non-characteristic symptoms of the the European Vipera spp. envenomings were present in our case report of a patient following a Vipera berus bosniensis bite, which occured in South-Western Hungary?

8. Which unique clinical signs of snakebite neurotoxicity could be observed in our patient following Vipera berus bosniensis envenoming?

9. Do the neurotoxic components of Vipera berus bosniensis cause a disturbance in the neuromuscular junctions?
   If so, how can this disturbance be objectively observed?

10. What is the possible explanation for the slowly evolving and prolonged neurological manifestations observed in our patient following the snakebite?

11. What are the clinical implications of our case report in the treatment of snakebites at the Emergency Department?
3 Materials and Methods

Regarding the study on ECG alterations in normokalemic and hyperkalemic patients

3.1 Study design

This was an observational retrospective study performed at the Emergency Center of the Kaposi Mőr General Hospital in 2013. The study received ethical approval from the regional ethical committee, the Institutional Ethics and Research Ethics Committee of the Somogy County Kaposi Mőr Teaching Hospital prior to the research procedure (Reference number: IG/02401-002/2015)

3.2 Patients

The annual census of the Emergency Center is approximately 35 000 patients and 80% of the patients are over 18 years of age. The medical records of adult patients admitted to the Emergency Center between 01.01.2013.-31.12.2013 were chosen randomly from the database of the Emergency Department. We selected 180 patients with normokalemia (3.4-5.1mmol/l) and 182 patients with moderately (6.0-7.0 mmol/L) or severely (>7.0 mmol/L) elevated serum or plasma potassium levels, randomly. All patients chosen for our study were adults, over 18 years of age. Patients were required to have had an ECG performed within one hour of the laboratory draw. The drawing of the blood and the storage and transport of the blood samples adhered to the regulations of the Emergency Center in order to prevent obtaining false test results. Laboratory analysis of the blood samples was intiated within 30 minutes of the blood draw. Patients with hemolysed samples were not included in the study. From the hyperkalemic group, patients with preanalytical errors (15 patients) and patients whose ECG recordings could not be completely analyzed due to technical reasons (16 patients) were excluded as well as patients with multiple presentations (16 cases) within the given interval. Only the first presentation to the Emergency Center was included. In the group with normokalemic patients, 10 patients were excluded due to missing ECG or missing potassium values. Finally, electrocardiograms and data from 135 hyperkalemic (moderate hyperkalemia n=97, severe hyperkalemia n=38) and 170 normokalemic patients were analyzed.
3.3 Laboratory tests

Potassium levels were measured in the Central Laboratory of the Moritz Kaposi General Hospital with Cobas 8000-C702 module according to the protocol of the manufacturer (Roche Diagnostics International AG, Switzerland). The normal range of the potassium level was 3.4-5.1 mmol/l. Point-of-care measurement of potassium was not available, and therefore not used in our study.

3.4 Study protocol

Data including the medical history, comorbidities and medication record were abstracted from the electronic medical record of the hospital. The following data were gathered from each record: demographics (age, gender), serum and plasma potassium levels, ECG, laboratory values (creatinine) obtained on same draw as the potassium level, comorbidities of the patients at the date of admission, medication taken by patients prior to obtaining the ECG, occurrence of cardiac arrest. Data was independently reviewed by two investigators.

3.5 ECG analysis

The ECG curves of each patient – recorded within one hour of the blood draw - were analyzed by two board-certified emergency physicians, independently. Since multiple ECG instruments were used, ECG-machine based ECG interpretations were not included in the study. The resulting varied ECG interpretations would have led to inaccuracy in the evaluation of the ECGs. The physicians were blinded to the objectives and method of the study, to all of the laboratory values (including potassium values), the particular clinical diagnoses and medical histories as well as to each other’s readings. Neither reader was a caregiver for any of the study subjects. Each ECG was examined for the following: rhythm, heart rate, PR interval, AV block, length of QRS interval, ST-T alterations, length of QTc interval. Cardiac arrest was documented in cases of pulseless electrical activity, pulseless ventricular tachycardia, ventricular fibrillation or asystole. PR interval was considered “prolonged” if PR duration> 200ms, QRS interval was considered “wide” if the QRS duration was > 110ms. QTc interval was deemed short if QTc<350ms and prolonged, if QTc> 450ms. The intervals used in our study were based on previous literature on ECG analyses (55) T waves were considered peaked if they were symmetrical and had a large amplitude based on the investigating physician’s judgement. ECG alterations were considered suggestive of
hyperkalemia if the following were recorded: AV junctional escape rhythm, Ventricular escape rhythm, bradycardia, Ist-IIInd-IIIrd degree AV blocks, wide QRS, peaked T-waves. Although not generally considered typical ECG manifestations of hyperkalemia, the following ECG changes were also recorded: atrial fibrillation, ST depression, short QTc and prolonged QTc.

3.6 Statistics

Data was analysed using SPSS22 software. In order to test for association of each parameter with measured potassium values, $\chi^2$ test, or Fischer exact tests were used as appropriate. P values ≤0.05 were considered to be statistically significant.
4 Results

Related to the study: ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic patients

4.1 Patient characteristics

Data was collected from 135 hyperkalemic (potassium > 6.0 mmol/l) and 170 normokalemic (potassium 3.4–5.9 mmol/l) patients. Gender distribution between the two groups was similar. Patients in the hyperkalemic group were older than patients in the normokalemic (control) group. Almost a third (29.6%) of the hyperkalemic patients suffered from chronic kidney disease (CKD), while only 8.8% of the normokalemic patients had CKD. Accordingly, preceding renal replacement therapy among hyperkalemic patients was significantly more frequent than among normokalemic patients. Regarding medication, a significantly higher percentage of hyperkalemic patients took angiotensin receptor blockers, angiotensin converting enzyme inhibitors, non-steroid analgesics, potassium supplements, and diuretics such as amiloride and spironolactone and other diuretics, like furosemide and thiazides (data not shown) than normokalemic patients. Comorbidities, such as heart failure, diabetes mellitus, liver failure, sepsis, cancer and dehydration were also significantly more prevalent in hyperkalemic patients. There was no significant difference between the prevalence of hypertension between normo- and hyperkalemic patients. Mortality within 72 hours of admission was high (13.3%) in the hyperkalemic group compared to only 2.4% of normokalemic patients. Data regarding patient characteristics are shown in Table 3.
<table>
<thead>
<tr>
<th></th>
<th>Control (n=170)</th>
<th>Hyperkalemia (n=135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.45± 15.95</td>
<td>70.61± 13.93</td>
</tr>
<tr>
<td>Female</td>
<td>54,7%  93</td>
<td>51,9%  70</td>
</tr>
<tr>
<td>Prior CKD</td>
<td>8,8%  15</td>
<td>29,6%*  40</td>
</tr>
<tr>
<td>Prior RRT</td>
<td>1,2%  2</td>
<td>7,4%*  10</td>
</tr>
<tr>
<td>Exit in 72h</td>
<td>2,4%  4</td>
<td>13,3%*  18</td>
</tr>
<tr>
<td>need of RRT</td>
<td>0,0%  0</td>
<td>15,6%*  21</td>
</tr>
<tr>
<td>HF</td>
<td>11,8%  20</td>
<td>32,6%*  44</td>
</tr>
<tr>
<td>DM</td>
<td>20,6%  35</td>
<td>36,3%*  49</td>
</tr>
<tr>
<td>HT</td>
<td>64,1%  109</td>
<td>73,3%  99</td>
</tr>
<tr>
<td>Liver failure</td>
<td>4,1%  7</td>
<td>11,1%*  15</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1,2%  2</td>
<td>14,8%*  20</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>14,1%  24</td>
<td>29,6%*  40</td>
</tr>
<tr>
<td>Dehydration</td>
<td>10,0%  17</td>
<td>31,1%*  42</td>
</tr>
<tr>
<td>B-blocker</td>
<td>38,8%  66</td>
<td>45,9%*  62</td>
</tr>
<tr>
<td>Digitalis</td>
<td>4,1%  7</td>
<td>5,9%  8</td>
</tr>
<tr>
<td>ACEi</td>
<td>37,6%  64</td>
<td>54,8%*  74</td>
</tr>
<tr>
<td>ARB</td>
<td>10,6%  18</td>
<td>14,1%*  19</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>4,7%  8</td>
<td>15,6%*  21</td>
</tr>
<tr>
<td>Amilorid</td>
<td>1,2%  2</td>
<td>14,1%*  19</td>
</tr>
<tr>
<td>NSAID</td>
<td>8,2%  14</td>
<td>16,3%*  22</td>
</tr>
<tr>
<td>K suppl</td>
<td>15,3%  26</td>
<td>35,6%*  48</td>
</tr>
</tbody>
</table>

Table 3: Baseline characteristics of normokalemic (control) and hyperkalemic patients. (CKD: chronic kidney disease, RRT renal replacement therapy, HF: heart failure, DM: diabetes mellitus, HT: hypertension, K suppl: potassium supplementation, * : p≤0.05)
4.2 The frequency of ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic patients

The frequencies of ECG alterations suggestive of hyperkalemia were recorded in patients with normokalemia, moderate hyperkalemia and severe hyperkalemia.

In the control group, 24.0% of normokalemic patients had ECG alterations suggestive of hyperkalemia and from these, 20% had one and 4% had 2 or more ECG changes indicative of hyperkalemia. Less than half of the patients (46%) with moderate or severe hyperkalemia had some form of ECG manifestation suggestive of hyperkalemia. 29% of severely hyperkalemic patients had no ECG changes indicative of hyperkalemia. From the 46% of hyperkalemic patients exhibiting some form of hyperkalemic ECG manifestation, 30% had one and 16% had two or more ECG alterations suggesting hyperkalemia. (*Table 4, Figure 4*)

<table>
<thead>
<tr>
<th>ECG alteration</th>
<th>1 ECG alteration (%)</th>
<th>≥2 ECG alterations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td>20%</td>
<td>0.0%</td>
</tr>
<tr>
<td>AV junctional escape</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Ventricular escape</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6.5%</td>
<td>7.1%</td>
</tr>
<tr>
<td>I\degree AV-block</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>II\degree AV-block</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>III\degree AV-block</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Wide QRS</td>
<td>8.2%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Peaked T-waves</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

*Table 4: Frequency of ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic (moderate and/or severe) patients (*: p≤0.05), Cardiac arrest included asystole, ventricular fibrillation, pulseless ventricular tachycardia and pulseless electric activity.*
Figure 4: The frequency of single and multiple ECG alterations suggestive of hyperkalemia in normokalemic and hyperkalemic patients

Significantly more patients with severe hyperkalemia had wide QRS (31.6%), bradycardia (18.4%), peaked T-waves (18.4%) and 1st degree AV block (18.4%) compared to normokalemic patients (8.2%, 6.5%, 4.7%, and 7.1%, respectively). Wide QRS (31.6%) was the most common ECG alteration in severely hyperkalemic patients and in the normokalemic group as well. *(Table 4, Figure 5.)* There was no significant difference in the frequency of ECG alterations suggestive of hyperkalemia between the normokalemic and the moderately hyperkalemic groups. *(Table 4, Figure 5)*
Figure 5: The frequency of ECG alterations suggestive of hyperkalemia in normokalemic, moderately hyperkalemic and severely hyperkalemic patients (*: p<0.05 vs control, #: p<0.05 vs moderate hyperkalemia) A: Peaked T waves; B: Wide QRS; C: Ist degree AV block; D: Bradycardia
When normokalemic patients were compared to all (moderately + severely) hyperkalemic patients, we found that wide QRS (18.5%) was the only ECG alteration significantly more frequent in all hyperkalemic patients compared to normokalemic patients (8.2%). AV junctional rhythm was seen only on the ECG of hyperkalemic (moderate or severe) patients but was not present on ECG recorded for normokalemic patients. (Table 4, Figure 5)

Cardiac arrest occurred in 8 patients with hyperkalemia and 5 of these patients had severely high potassium levels. None of the patients with normal potassium levels had cardiac arrest. (Table 4)

4.3 The frequency of ECG alterations possibly associated with hyperkalemia in normokalemic versus hyperkalemic patients

Frequency of ECG abnormalities possibly associated with hyperkalemia including atrial fibrillation, QTc changes and ST depression were registered.

There was no significant difference regarding the frequency of ST depression between patients with normal or increased levels of potassium. Atrial fibrillation was significantly more frequent in severely hyperkalemic patients (26.3%) compared to normokalemic patients (10.6%). However, no significant difference regarding atrial fibrillation was detected between the moderately hyperkalemic and the normokalemic groups. Prolonged QTc was the only ECG alteration which was significantly more prevalent in both patients with moderate (17.5%) and severe hyperkalemia (21.1%) compared to patients with normokalemia (5.3%). (Table 5, Figure 5).
<table>
<thead>
<tr>
<th></th>
<th>AF</th>
<th>ST depression</th>
<th>Short QTc</th>
<th>Prolonged QTc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=170)</td>
<td>%</td>
<td>10.6%</td>
<td>28.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>18</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td><strong>All hyperkalemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=135)</td>
<td>%</td>
<td>15.6%</td>
<td>23.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>21</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperkalemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=97)</td>
<td>%</td>
<td>11.3%</td>
<td>22.7%</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>11</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperkalemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=38)</td>
<td>%</td>
<td>26.3%*</td>
<td>23.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>10</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5: The frequency of ECG alterations possibly associated with hyperkalemia in normokalemic versus hyperkalemic patients. (*: p≤0.05)

4.4 The association between the occurrence of certain ECG alterations and the severity of hyperkalemia

We investigated whether the elevations of potassium levels increased the occurrence of certain ECG alterations. The following differences were found between moderately and severely hyperkalemic patients: atrial fibrillation (11.3 vs 26.3%, $\chi^2$ test, p<0.05), $I^o$ AV block (4.1% vs 18.4%, Fisher exact test, p<0.05), wide QRS (13.4% vs 31.6%, $\chi^2$ test, p<0.05) and peaked T waves (6.2% vs 18.4%, Fisher exact test, p=0.05) were present more frequently on the ECG recordings of patients with severe hyperkalemia than on the ECG of patients with moderate hyperkalemia. (Figure 5, Figure 6)
Figure 6: The frequency of ECG alterations possibly associated with hyperkalemia in normokalemic versus hyperkalemic patients

4.5 Report of a patient following V. b. bosniensis envenomation

Case report

A 63-year-old man was bitten by an adder in Kaszó, Somogy County, South-Western Hungary on May 04th, 2017 between 13:30 and 13:45. Medical history of the patient included sinus bradycardia (heart rate: 45/min) diagnosed in 2015 and hypertension. The latter condition was controlled by Tolura® (telmisartan, 80 mg daily). He had had a normal coronary angiogram in 2014. He had no known allergies and had not suffered any snakebites previously. He took his telmisartan tablet on the morning of the accident. The patient indicated he did not consume alcohol preceding the incident or on a regular basis.
The patient found a uniformly black snake in his garden which he wanted to show his wife before removing it. The snake bit the patient’s left index finger when he grabbed it. A burning pain developed immediately at the site of the bite. Although the patient knew that he was bitten by a viper – because of the burning pain emerging immediately – he was not certain about the exact species and did not want to risk another bite, therefore he preserved the specimen for exact identification and took a photograph of it. The animal was later identified by an expert as a sub-adult, melanistic specimen of *V. b. bosniensis* (length was about 38-40 cm) based on the native distribution area of the taxon and the photograph taken (*Figure 2 C*). The patient immediately started to squeeze the blood out of the bite site. He experienced sweating and nausea combined with stomach ache in the first 10 minutes following the snakebite. His wife transported him by car to the nearest hospital in Nagyatád. He vomited three times during the transport.

Upon arrival (at 14:10) at the hospital in Nagyatád two fang marks were clearly identifiable on the proximal nail fold of the left index finger. A small local haematoma and minimal local swelling were visible around the fang marks. The patient complained of nausea and dizziness and vomited once more. He also complained of abdominal pain during the medical examination. A blood pressure reading of 120/80 mmHg was recorded with mild tachycardia (90/min). An ECG was performed at 14:21, showing horizontal ST depression in leads V5-6 (*Figure 7*).

![Figure 7: ECG changes of patient showed transient horizontal ST depression in V5-6.](image)

*The patient’s date of birth and name are blinded by black rectangle.*
Isolyte infusion (500 ml) and antiemetic medication (metoclopramide, 10 mg i.v.) were given. The patient was transferred by ambulance to the Emergency Department of Somogy County “Moritz Kaposi” General Hospital in Kaposvár. The abdominal muscles were very tender, and guarding was detected upon palpation on the way to the hospital. He vomited again in the ambulance. The following blood pressure, heart rate and oxygen saturation levels were recorded during the transportation: 160/100 mmHg, 77/min, 98% (14:35); 166/105 mmHg, 71/min, 98% (14:40); 165/105 mmHg, 69/min, 98% (14:50); 160/100 mmHg, 69/min, 98% (15:00).

Upon admission (at 15:05) at the Emergency Center of Somogy County “Moritz Kaposi” General Hospital in Kaposvár the patient was pale, weak and sweating. He still complained of nausea. His consciousness remained normal and the patient was able to answer questions adequately. The last digit of the bitten finger was swollen. The following vital parameters were recorded: blood pressure: 140/70 mmHg; heart rate: 74 /min; SO₂: 98 %, body temperature 36.5°C. The initial routine laboratory findings included: serum potassium 3.39 mmol/l (normal range: 3.70-5.40); absolute neutrophil count 8.52 g/l (normal range: 2.00-8.50), and blood glucose 9.4 mmol/l (normal range: 3.3-5.5). In the first 30 minutes of observation the patient vomited twice. Tenderness of the abdominal muscles was replaced by intense abdominal colic and the patient developed profuse diarrhoea (produced high volume, loose stools on two occasions). The patient was admitted to the Intensive Care Unit of the Emergency Department. The hypersensitivity skin test (at 15:28) yielded negative results; antivenom therapy (500 IU i.m. Viper Venom Antitoxin®, Biomed, Warsaw (monovalent antivenom, V. berus venom is used in its production)) was applied at 15:48. As supportive care the patient received chloropyramine (20 mg i.v.), and methylprednisolone (125 mg i.v.). Debridement (cleansing with aqueous solution of 10% povidone-iodine and hydrogen peroxide solution) and anaesthesia (nerve block by Oberst’s method) were performed locally followed by removal of the superficial tissues around the fang marks on the bitten finger (Figure 8).
The next morning (05 May, at 08:20) the patient was unable to open his eyes. When raising the upper eyelids manually, he reported constant double vision. He reported that the images seen before him were displaced horizontally. He was unable to move his eyes upward. The pupils were equal in size and moderately dilated, the pupillary light reflexes were intact. Complete bilateral ptosis with external ophthalmplegia was diagnosed on neurological examination (Figure 9).
Figure 9: Complete bilateral ptosis and ataxic nystagmus in the patient. (A): Gaze to right, abducted right eye shows paralysis of left medial rectus. (B): Gaze to left, abducted left eye shows paralysis of right medial rectus. (C) and (D): The eyeballs diverged both horizontally and vertically while looking ahead. (E): The left eye did not cross the midline when the patient attempted to look to the right, whereas the right eye did not cross the midline when he attempted to look to the left. (Photographs were taken by Dr Gergely Bilics. The patient verbally contributed to taking and publishing of photos.)

The eyeballs diverged both horizontally and vertically while looking ahead. The left eye did not cross the midline when the patient attempted to look to the right, whereas the right eye did not cross the midline when he attempted to look to the left. At 10:30, single-fiber electromyography (SfEMG) was performed following neurological consultation. The SfEMG record is shown in Figure 10.
Figure 10: A pair of action potentials recorded from the envenomed patient during voluntary activation of the right orbicularis oris muscle. The oscilloscope is triggered by the rising portion of the first potential, which falls at the same position with each discharge. Legend: (A): Consecutive discharges are superimposed. (B): The second potential falls at varying positions (black dots) among successive discharges, demonstrating the neuromuscular jitter. The sweep is triggered on the first potential, and increased jitter is seen in the second potential. Gain: 500mV/div, sweep time: 0.5 ms/div

By 12:56 the localised swelling on the bitten finger was not apparent any more. At 16:00, the patient received neostigmine-methylsulfate (0.5 mg i.v.) in infusion and an atropine-sulfate (0.5 mg i.m.) injection. The laboratory findings are listed in Table 6.
Table 6: Detected changes in the patient's laboratory values during the course of envenoming

On 06 May, the patient felt weak and still had ptosis but he was already able to open his eyelids to uncover the pupils. He complained of severe double vision, intense dizziness, and felt “drunk”. Although he was able to walk obvious signs of imbalance and unsteady gait were apparent. The vital parameters remained stable. By the end of 07 May, the ptosis resolved, ophthalmoplegia started to resolve but the patient was still experiencing double vision. No new medical event occurred during the night.

On 08 May (at 09:20), the ptosis resolved as well as the paralysis of the extraocular muscles. He reported double vision only on sudden lateral gaze (at this stage the image seen was “delayed”). The patient was discharged from hospital with stable vital parameters at 14:00. The medicinal therapy recommended for home included benfotiamin (300 mg daily). The patient's diplopia - as the last symptom of the envenoming - resolved completely on 13 May based on the follow-up information obtained from the patient by the physician treating the patient.
5 Discussion

5.1 Discussion related to the study on: “ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic patients”

Hyperkalemia is one of the most common, potentially life-threatening metabolic disorders of reversible periarrest conditions that needs to be recognized and treated in time (56). Potassium levels above the normal range often remain unnoticed and periarrest situations may occur without warning (57). The recognition of patients with hyperkalemia poses challenges and there are often delays in the initiation of the electrolyte disorder’s treatment. According to a study conducted in an Emergency Department in the U.S., the mean time from triage to treatment of patients with potassium levels 6 mmol/l or above, was 117 minutes. (26). Furthermore, a mean 1-hour- long delay between the time of laboratory notification of hyperkalemia and initiation of treatment was found, despite recommendations for “immediate therapy” for serum potassium levels over 6 mmol/l (26, 58). Based on a review of the medical charts, underlying reasons for the delay were found to be: diagnostic uncertainty (in many cases the physician’s reaction to an unexpectedly high potassium level was to repeat the blood test and to acquire an ECG) or the difficulties in obtaining intravenous access (26).

Electrocardiography is a widely used, easily attainable method to raise the possibility of hyperkalemia, however there have been conflicting reports about its sensitivity and specificity to signal elevated potassium levels (16, 26, 59). An earlier report by Wrenn et al. investigated whether physicians blinded to the serum potassium level could predict hyperkalemia from the ECG (59). The report showed that the ECG readers’ ability to predict the severity of hyperkalemia was poor (59). The sensitivities of the readers for predicting hyperkalemia were .43 and .34 and the specificities for detecting hyperkalemia were .85 and .86. (59). The study concluded that even in high-risk patients, the ECG was not a sensitive method of detecting hyperkalemia (59). A subsequent retrospective review of the frequency of ECG changes in hyperkalemia also found that the electrodiagram was insensitive for diagnosing hyperkalemia, although the probability of ECG changes increased with the elevation of serum potassium levels (25). Other reports stated that there was a predictable progression of ECG alterations with the elevation of serum potassium levels (16). The most recently conducted study by Rafique at al. in which 528 ECGs from ESRD patients were evaluated found that the ECG
was not a sensitive method of detecting hyperkalemia, but that its high specificity for detecting high potassium levels could be used as a rule in test. (60)

In our study we investigated whether ECG alterations suggestive of hyperkalemia were present in a randomly selected group of normokalemic patients admitted to the Emergency Center. ECGs have often been shown to be normal in hyperkalemia and a number of cases have been reported where patients with severely elevated potassium levels did not show typical ECG manifestations (27, 59). In accordance with these investigations, we found that less than half of the hyperkalemic patients exhibited ECG changes suggestive of hyperkalemia, while the majority of the hyperkalemic patients showed no typical ECG changes at all. A surprisingly high proportion (24%) of normokalemic patients exhibited ECG alterations suggestive of hyperkalemia. Thus, based on ECG analysis alone, normokalemia and hyperkalemia cannot be confirmed or excluded in patients.

A study conducted in the United States on hemodialysis patients with hyperkalemia investigated the prevalence of ECG changes in stable patients with ESRD (19). According to this study, none of the patients had arrhythmia or any of the typical electrocardiographic alterations suggestive of hyperkalemia and no significant difference was found in T-wave amplitude or T wave to R wave ratio although the total serum calcium concentration showed an inverse relation with T wave amplitude (19). Thus, it was concluded that hemodialysis patients with hyperkalemia may not show the usual ECG alterations, probably due to fluctuations in serum calcium concentration (19).

It must be noted, however in our study, that some ECG changes suggestive of hyperkalemia (wide QRS, peaked-T waves, 1st degree AV-block and bradycardia) were significantly more prevalent in the severely hyperkalemic group. Although there wasn’t a significant difference between the frequency of ECG alterations suggesting hyperkalemia in normokalemic and moderately hyperkalemic patients, the number of ECG alterations suggestive of hyperkalemia simultaneously present increased with the degree of serum potassium elevation. These findings are in line with a previous report on the higher frequency of ECG changes with increasing potassium levels (25). Peaked T waves are considered to be the typical earliest ECG signs of elevated serum potassium levels (16, 25, 26). In our study, peaked T-wave was the second most common ECG manifestation among severely hyperkalemic patients, while wide QRS was the most common ECG change and significantly
more often found among all hyperkalemic patients compared to patients with normal potassium levels.

We examined the prevalence of four ECG abnormalities, whose association with hyperkalemia has been found to be equivocal according to previous studies. ST depression may be an ECG manifestation of hyperkalemia (61), but we did not detect a significant difference in the frequency of ST depression between normokalemic and hyperkalemic patients in our study. Atrial fibrillation is the most frequently found sustained arrhythmia in the elderly and most studies have found that lower potassium levels were associated with a higher risk of atrial fibrillation (62-64). According to the results of the prospective population-based Rotterdam study, participants with hypokalemia (< 3.5 mml/l) had a higher risk of atrial fibrillation (62-64). This association was independent of age, gender, serum magnesium and other potential confounders (62-64). Our results showed, however, that atrial fibrillation was more prevalent in severely hyperkalemic patients compared to normokalemic patients. We attribute these results to the synergistic effect of two groups of diseases often present in patients with high potassium levels. Hyperkalemia and heart failure are common in chronic kidney disease and heart failure is often the cause of or caused by atrial fibrillation. Therefore, atrial fibrillation occurs not as the result of hyperkalemia but rather as the consequence of illnesses often associated with hyperkalemia.

Although shortening of the QTc interval in hyperkalemia has been reported in several investigations (61, 65), the possibility of prolonged QTc occurrence in hyperkalemia has also been raised (66). The results of a Japanese study investigating sudden cardiac death in hemodialysis patients implied that shifting of electrolytes, such as potassium and calcium during hemodialysis caused rapid prolongation of the QT interval after hemodialysis, which may have resulted in the onset of ventricular arrhythmia and sudden cardiac death (66). In our study, prolonged QTc was more frequent in severely hyperkalemic patients compared to normokalemic patients. In fact, prolonged QTc was the only ECG alteration significantly more frequent in both moderately and severely hyperkalemic patients compared to the group with normal potassium levels. The high prevalence of heart failure in hyperkalemic patients and the effect of drugs on the length of QTc may contribute to these results, similarly to our observation regarding atrial fibrillation. Although the reasons underlying our findings need to be clarified, the results imply that prolonged QTc and atrial fibrillation could also draw attention to hyperkalemia, besides the more acknowledged ECG manifestations of hyperkalemia. It is important for clinicians to be aware of the changing trend (e.g. higher
prevalence of heart disease, frequent application of certain drugs) of the clinical presentations of hyperkalemic patients.

Our study has other implications. When we compared baseline data from patients in the normokalemic and hyperkalemic groups, CKD and comorbidities such as heart and liver failure were significantly more frequent in hyperkalemic patients. CKD and/or hemodialysis have been known to increase the likelihood of hyperkalemia (19, 25) and so patients suffering from renal failure are more at risk of developing potassium cardiotoxicity (10). Within a decade there were twice as many cases of chronic renal failure in the United States attributed to hypertension and diabetes mellitus (26). Hyperkalemia was observed in the predialysis blood testing of patients requiring hemodialysis in 10% of the cases (26). Mortality from hyperkalemia could be attributed to 3-5% of patients receiving dialysis (67). The rising number of patients with chronic renal disease is predicted to increase the number of cases with hyperkalemia (26). Patients from the geriatric population are particularly prone to developing hyperkalemia, due to age-related decline in glomerular filtration rate, impaired rennin-angiotensin-aldosterone axis, higher number of comorbidities and the consumption of multiple medications (68).

The pharmacological treatment of patients with different kinds of cardiovascular diseases may also contribute to the rising number of hyperkalemic patients. Patients with medical conditions such as Type 2 DM and congestive heart failure are often treated with medication such as ACE-inhibitors (26). The application of certain types of medication, including ACE-I, ARB and potassium-sparing diuretics has been associated with an increased number of hyperkalemia-related hospitalizations and mortality (5, 69-71). Diuretics are among the most frequently prescribed drugs. Following the publication of the Randomized Aldactone Evaluation Study (RALES), for example, an increasing number of patients were hospitalized for hyperkalemia, which was thought to be the consequence of the more frequent prescription of spironolactone (26). In a Swiss cross-sectional analysis of patients presenting to the Emergency Room, it was demonstrated that the prevalence of hyperkalemia was linked to the number of diuretic agents taken by patients (69). In this study, all types of diuretics were associated with an increased prevalence of hyperkalemia (69). Hyperkalemia also often occurs as a consequence of drug-drug interactions such as due to the application of ACE-inhibitors with potassium-sparing diuretics (72).
In keeping with these earlier reports, we found in our study that the application of these types of drugs was also more common in patients with elevated potassium levels. Our data underline the importance of regular monitoring of electrolytes in patients taking hyperkalemia-inducing medication, preferably already in non-urgent situations within the primary care setting since ECG diagnosis of hyperkalemia is uncertain.

To our knowledge, this study is the first to investigate ECG alterations suggestive of hyperkalemia in a large number of patients with normal potassium levels. Besides supporting evidence for the unreliability of ECG diagnosis in hyperkalemia, our results show that a fourth of normokalemic patients also exhibit ECG alterations suggestive of hyperkalemia. This indicates that treatment of suspected hyperkalemia in the prehospital setting, prior to laboratory confirmation of potassium levels, may not be prudent. Although it has been suggested that initiation of life-saving treatment with calcium in suspected hyperkalemia prior to laboratory confirmation of hyperkalemia would be advisable, we disagree with this proposition (73). Investigations have shown, that the empiric treatment of hyperkalemia based on ECG alone was predicted to lead to the mistreatment of at least 15% of patients (59) and treatment decisions should not depend only on the presence of ECG alterations (25).

Limitations:

Our study has several limitations. The normokalemic (control) group and hyperkalemic group were not matched regarding age, medication and comorbidities. This was to be expected, however, as this investigation was a cross-sectional study of patients admitted to emergency care. The interpretation of ECGs may be another confounding factor, since a number of ECG alterations can be due to other causes than hyperkalemia or alternatively, ECG changes due to other conditions may mask signs of hyperkalemia. We argue, however, that in the prehospital, emergency setting information regarding medication and previous illnesses is not readily available to the caregiver and therefore, he or she must make decisions regarding diagnosis and treatment with none or very limited information. Another limitation of our study is that although the investigation was conducted on a relatively large number of patients, a larger-scale study examining the ECG alterations suggestive of hyperkalemia in normokalemic patients would be needed to confirm our results.

Our findings imply, what previous studies have suggested, that the ECG is not a reliable tool in the diagnosis of hyperkalemia. To this, our study adds valuable information by
demonstrating that a minority of patients with normal potassium levels may also exhibit ECG alterations considered to be typical for hyperkalemia. These results underline the importance of accurate laboratory-confirmed diagnosis of hyperkalemia prior to initiation of treatment. Nevertheless, since ECG alterations suggestive of hyperkalemia are more frequent in hyperkalemic patients, any change in the ECG attributable to hyperkalemia should draw attention to a potentially life threatening condition, in the prehospital emergency setting, especially in periarrest situations.

5.2 Discussion related to the “Case report of V.b.bosniensis envenomation”

Although snakebites are relatively rare in Hungary, their medical importance is unquestionable, since envenomation can cause severe symptoms and can even have life-threatening effects. Hospital admission may be delayed due to the remoteness of certain subspecies’ habitats (74). Routine antivenom administration, without necessary individualisation of therapy due to the lack of information regarding the characteristics of the given snakes’ venom may expose patients to higher risks of complications (74). Studies of neurotoxicity following snakebites are challenging, since there are large differences between individual patients in the clinical manifestations following envenoming of particular species. Comparing results from different studies is difficult since there is no uniform description or grading scale of neuromuscular weakness. The majority of our knowledge regarding snakebites from the literature comes from case reports.

Our case report focuses on the clinical presentation of a particular V. b. bosniensis bite which occurred in South-Western Hungary, the neurotoxic features of which resulted in the same peripheral neuromuscular paralytic symptoms that are typical of humans bitten by vipers in Southern and South-Eastern Europe. However, certain characteristics of our case differed from the common features of the European Vipera spp. envenomings.

The immediate local burning pain the patient experienced indicated that venom had been injected, although V. b. bosniensis bites can be relatively painless (74). The minimal hematoma was consistent with the previously reported local symptoms in the Bulgarian as well as the South-Western Hungarian and Northern Croatian cases (74, 75). Relatively mild local venom effects characterizing the envenomings by these adders have already been
described by Reuss (47). Minimal local swelling with prolonged and marked systemic symptoms is atypical for the bites of the other European Vipera spp. Mild local symptoms cannot exclude moderate and severe envenomings caused by V. b. bosniensis, as is illustrated by our case.

In other cases, the local symptom of edema, which may be considered mild compared to systemic symptoms, can prove life-threatening. A previous case report described how the envenomation by V. berus of a patient, bitten on the tongue compromised the patient’s airway causing severe hypoxemia, circulatory failure and an impaired level of consciousness (76).

The early onset dizziness and perspiration were probably due to anxiety and sympathetic overactivity. Psychological trauma often occurs after venomous snakebites (77). Nausea, vomiting and diarrhoea develop frequently in V. berus envenomings and are considered to be an early “anaphylactoid reaction” (39). The intensity and repeated occurrence of these symptoms indicate severe envenoming (77) just as in our case. Stomach ache and abdominal discomfort are commonly experienced and are often followed by diarrhoea (40). In case of extremely intensive pain, venom-induced acute abdominal catastrophe can be suspected (39). Our patient had painful abdominal guarding followed by colic and diarrhoea without any abdominal complications. All gastrointestinal symptoms ceased promptly and completely after antivenom administration. Similar abdominal symptoms were reported in a Bulgarian V. b. bosniensis envenoming (74).

Cardiovascular venom effects are the most commonly encountered features of V. berus envenomings in the whole European distribution range of the species. Arterial hypotension is a significant systemic manifestation of V. b. berus bites (39, 40, 78) but is also a known feature of V. b. bosniensis envenomings (75). However, envenomed patients may develop high blood pressure after being bitten by specimens belonging to certain populations of both subspecies (75, 79, 80). Hypotension, as well as hypertension often develop in the first two hours of the envenoming, and may be transient, persistent and/or recurrent (39, 75, 79-81). Our patient’s transient high blood pressure might have been related to venom effects. The patient’s blood pressure was normal (120/80 mmHg) initially (the patient took telmisartan in that morning) but then it suddenly increased, and this was followed by further episodes of high blood pressure during the course of the envenoming (in the early phase: 120/80-165/105 mmHg, and during hospitalization: 115/85-140/70 mmHg).
Venom of *V. b. berus* is considered potentially cardiotoxic (82) and cardiac complications are often recorded in such envenomings (39, 40, 78, 80). Arrhythmias are known to occur in those bitten by *V. b. bosniensis*. Reuss was the first to mention clinically significant arrhythmias and heart block in severe cases (75). The wide range of cardiac manifestations following the bite of both subspecies suggests that the transient horizontal ST depression and tachycardia detected in the case of our patient may have been due to the effect of the venom.

Neurotoxicity may be expected following the bite of specimens from certain populations of *V. b. berus* in the Carpathian Basin (79, 83) and *V. b. bosniensis* (47, 48, 74, 75, 84). In *V. b. bosniensis* envenomings, peripheral neurotoxicity involving mainly cranial nerve disturbances and gait incoordination are typical neurological manifestations (74, 75). In the case series reported by Westerström et al, diplopia, ptosis were described, whereas Častven (84) reported bulbar paralysis following Serbian *V. b. bosniensis* bites. These neurological signs and symptoms have been attributed to venom phospholipase A$_2$s (PLA$_2$s) (85). Complete or partial third nerve (oculomotor) palsy may occur, with symptoms of ophtalmoplegia due to the neurotoxic effect of the venom on the superior, medial and inferior rectus, inferior oblique and levator palpebrae superioris muscles of the eye. Ptosis is often associated with either partial or complete ophthalmoplegia, which are frequently diagnosed not only in *V. b. bosniensis* envenomings (74, 75) but also following the bites of specimens belonging to neurotoxic populations of *V. ammodytides* in Croatia, Bulgaria, and Slovenia, and *V. aspis* in France and Italy, respectively (41, 86-89). Snakebite neurotoxicity causes typical descending neuromuscular paralysis in humans (90). Extraocular muscles are affected earlier than skeletal muscles by venom neurotoxins presumably because of the peculiar structure of their neuromuscular junction and muscle-nerve ratio (90). Envenomed patients may show ataxic nystagmus in both lateral directions (91). This unique clinical sign of snakebite neurotoxicity combined with complete extraocular muscle palsy, was observed in our case.

Previously, a report described the case of a young man bitten on the forehead by a European adder (92). The resulting edema and petechial haemorrhages resolved after a few days but unilateral facial frontal paresis and ptosis persisted. Three weeks after the snake bite facial frontal paresis was still present and electromyography of the muscle initiated spontaneous fibrillation. Furthermore, unilateral ptosis was still present one year after the bite (92).
Due to the weakness of the facial and extraocular muscles in our patient the individual muscle fibers failed to contract intermittently, thereby producing signs of neuromuscular block on sfEMG. This finding adds a valuable piece of information to the medical literature of snakebites, as the available data about sfEMG studies performed in patients showing neuromuscular paralysis following snakebite is quite limited.

If the snake’s venom contains prejunctional neurotoxic PLA$_2$s, the neuromuscular paralysis develops slowly and takes longer to recover (93). These patients show poor response or resistance to antivenom therapy and acetylcholinesterase inhibitors (94). Nevertheless, in our case there was a compelling urge to use antivenom therapy with respect to the massive gastrointestinal symptoms and the ECG changes. According to previous reports, edrophonium (Tensilon test) can be used to prognosticate the response to treatment with the longer-acting neostigmine, if the neuromuscular blockade caused by the venom is post-synaptic (95). In the case of our patient, neostigmine was applied on the day following the bite in an attempt to ameliorate the neurological signs and symptoms. The patient also received atropine to avoid the potential side effects of neostigmine. The slowly evolving and prolonged neurologic manifestations, the lack of benefit from the antivenom and neostigmine therapy applied with regards to the neurotoxicity, strongly suggest that the venom of the South-Western Hungarian V. b. bosniensis contained prejunctional neurotoxic PLA$_2$(s), as suggested previously by Malina et al. (79). The neurotoxic effects were observed in our patient. Interestingly, according to a most recent investigation, in which the toxicological profile of V. aspis and V. berus venoms were tested in vivo in mice, it was shown that both venoms contain enzymatically active PLA$_2$, but only the venom of V. aspis was demonstrated to be neurotoxic (29). The effect of the neurotoxin was shown to be due to the degeneration of peripheral nerve terminals at the neuromuscular junction and V. berus venom was shown to cause a haemorrhagic effect (29). The explanation for the discrepancy between the results of this study and previous case reports, along with our patient’s case is currently unclear but could be explained by two possible hypotheses; one being the experimental characteristic (experiments in mice) of this recent study by Zanetti et al. (29), as opposed to human cases of snake bites, and the other hypothesis being that differences between neurotoxicity were found due to intraspecies venom variability.

*Viper Venom Antitoxin* was given to the patient in our case. To date there are very few preclinical comparative data and no randomised controlled trials evaluating the efficacy of
antivenoms against different vipera species. (96) The previous review on antivenoms suggested the efficacy of Zagreb, ViperFAV and Viper Tab in clinical studies. (96) Based on the earlier case described by Malina et al. (79) as well as our patient’s case, it would be prudent to consider the use of polivalent antivenoms, such as Zagreb in the antivenom therapy of V. b. bosniensis snake bites, due to the high venom component variability between the individual snakes.

Based on the new classification of Vipera spp. envenomings (97), our patient’s case can be categorized as moderate or severe, although, certain atypical features made grading difficult.

The laboratory findings were compatible with those usually seen in V. berus envenomings. Slight abnormalities in the haemostatic parameters combined with mild local symptoms were consistent with the previously reported cases (75) and similar to the Eastern Hungarian neurotoxic V. b. berus envenomings (79, 83). In Bulgaria, a severe neurotoxic V. b. bosniensis bite resulted in a slightly reduced haematocrit value (39%), leukocytosis (absolute neutrophil count: 12.2 G/L) and elevated blood glucose level only (Boyan Petrov, pers. comm., 2017; without full details by Westerström et al., (74)). Haematological changes of any kind were not reported in neurotoxic bites of V. b. bosniensis in Serbia (84). Taking into account the clinical significance of venom composition variability not only between the different adder populations but also at the intra-populational level as it was described in V. b. berus (44), the potential existence of venom composition differences is not negligible in South-Western Hungarian adders, either. Additionally, an inverse correlation can be probable between the neurotoxic and the proteolytic activity and/or protease content of venom in case of V. b. bosniensis, similarly to the specimens of a particular, Eastern Hungarian, neurotoxic V. b. berus population (44).

Our case study describes the consequences of V. b. bosniensis bite, which occurred in the northernmost geographical distribution range of the taxon. Certain uncommon features of this case – i.e. minor local venom effects combined with prolonged and marked systemic symptoms and almost normal absolute neutrophil count – raise the issue of venom component variability within the geographical range of the Balkan adder and also between individual animals within the same population. On the other hand, classical signs and symptoms of descending neuromuscular paralysis associated with snakebite neurotoxicity developed in our patient affecting the 3rd, 4th, and 6th cranial nerves innervating the eye lid, the extraocular
and the facial muscles. The slowly developing and prolonged neurological manifestations and their unresponsiveness to acetylcholinesterase inhibitor and antivenom therapy indicate the presence of prejunctional PLA$_2$(s) in the venom of South-Western Hungarian adders. Our observations underline the importance of venom component variability of individuals within the same viper population, which should be taken into careful consideration when choosing the most appropriate antivenom therapy.
6 Conclusions

1. Hyperkalemic patients were older than patients in the normokalemic (control) group in our study. Almost a third (29.6%) of the hyperkalemic patients suffered from chronic kidney disease (CKD), while only 8.8% of the normokalemic patients had CKD. A significantly higher percentage of hyperkalemic patients took angiotensin receptor blockers, angiotensin converting enzyme inhibitors, non-steroid analgesics, potassium supplements, and diuretics than normokalemic patients. Comorbidities, such as heart failure, diabetes mellitus, liver failure, sepsis, cancer and dehydration were also significantly more prevalent in hyperkalemic patients. Mortality within 72 hours of admission was significantly higher (13.3%) in the hyperkalemic group compared to only 2.4% of normokalemic patients.

2. 24% of normokalemic patients and 46% of patients with moderate or severe hyperkalemia had ECG alterations suggestive of hyperkalemia. 29% of severely hyperkalemic patients had no ECG changes indicative of hyperkalemia whatsoever.

3. Significantly more patients with severe hyperkalemia had wide QRS, bradycardia, peaked T-waves and 1st degree AV block compared to normokalemic patients. There was no significant difference in the frequency of ECG alterations suggestive of hyperkalemia between the normokalemic and the moderately hyperkalemic groups. When normokalemic patients were compared to all (moderately + severely) hyperkalemic patients, we found that wide QRS was the only ECG alteration significantly more frequent in all hyperkalemic patients compared to normokalemic patients.

4. Prolonged QTc was the only ECG alteration which was significantly more prevalent in both patients with moderate and severe hyperkalemia compared to patients with normokalemia. There was no significant difference regarding the frequency of ST depression between patients with normal or increased levels of potassium. Atrial fibrillation was significantly more frequent in severely hyperkalemic patients compared to normokalemic patients. The higher prevalence of both prolonged QTc
and atrial fibrillation in hyperkalemic patients raises the suspicion of covariance: that the simultaneous higher occurrence of heart failure and associated drug treatment may be responsible for our observations.

5. With the elevation of potassium levels from moderate to severe hyperkalemia, atrial fibrillation, I° AV block, wide QRS and peaked T waves were present more frequently, therefore a positive correlation could be detected between the frequency of these ECG alterations and the severity of hyperkalemia.

6. Our results imply that the ECG is not a reliable tool in the diagnosis of hyperkalemia, since severely hyperkalemic patients may have no ECG manifestations at all, while patients with normal potassium levels may also exhibit ECG alterations considered to be typical for hyperkalemia.

These findings underline the importance of accurate laboratory-confirmed diagnosis of hyperkalemia prior to initiation of treatment.

7. The envenoming by Vipera b. bosniensis of the patient in our case report caused characteristically mild local symptoms at the site of the bite but the prolonged and marked systemic symptoms, implying severe envenoming is not characteristic of envenomings caused by this Vipera ssp. Systemic symptoms included dizziness, vomiting, diarrhea, abdominal guarding, transient blood pressure elevations, transient horizontal ST depression on the ECG and symptoms of neurotoxicity.

8. We observed the unique clinical signs of snakebite neurotoxicity, complete extraocular muscle palsy and ataxic nystagmus, in our patient.

9. Using sfEMG, we found, that the individual muscle fibers in the facial and extraocular muscles in our patient failed to contract intermittently, which indicated that the snake venom induced neuromuscular blockage.

10. Due to the pronounced neurological disturbances and the lack of benefit from the antivenom and acetylcholinesterase inhibitor treatment and based on previous descriptions in the literature, we hypothesized that the observed neuromuscular blockage was due to the prejunctional PLA₂(s) present in the venom of South-Western Hungarian adders.
11. Our case report of *Vipera berus bosniensis* envenoming implies that non-characteristic features of snakebites may be expected due to the venom component variability within a population of *Vipera* ssp. Therefore, despite mild local symptoms at the site of the snake bite, healthcare professionals should be prepared for the treatment of moderate to severe systemic symptoms in patients following South-Western Hungarian adder envenoming. The particular type of antivenom treatment should also be carefully selected. Based on the experience of our case, and supported by others, due to venom component variability, the use of *polyvalent* antivenom treatment should be considered.

The study regarding the common medical condition of hyperkalemia and the case report of the relatively rare case of snake envenoming aptly demonstrate the challenges of decision-making in emergency medicine. In spite of the overcrowded workflow of the emergency department keen attention needs to be paid to each patient and priority given based on the urgency of each case.

**Limitations**

The findings of this thesis have to be considered in light of its limitations. The first is that out of the numerous different emergency cases we decided to choose one common and one rare medical condition instead of others. The second limitation concerns the methodology of the investigations. The study on hyperkalemic ECG alterations examined a larger number of patients, however, the second report illustrated the case of only one patient.
7 References


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34. Dudich E. Faunistic notes. Állattani Közlemények. 1928;25:44.


8 Publications

8.1 Publications related to the thesis

1. Csaba Varga; Zsolt Kalman; Aliz Szakall; Kata Drubits; Marton Koch; Robert Banhegyi; Tibor Olah; Eva Pozsgai; Norbert Fulop; Jozsef Betlehem. ECG alterations suggestive of hyperkalemia in normokalemic versus hyperkalemic patients. BMC EMERGENCY MEDICINE DOI: 10.1186/s12873-019-0247-0 (IF: 1.39)


IF in the topic: 3.742

8.2 Oral and poster presentations related to the thesis

1. Varga, Csaba
Kígyómarások kapcsán észlelt neurotoxikus tünetegyüttes
In: Betlehem, J; Radnai, B; Deutsch, K; Bánfai, B; Pandur, A; Schiszler, B; Tóth, B; Bánfai-Csonka, H; Talabér, K; Köcse, T; Horváth, B

Prevalence of iatrogenic hyperkalemia in the Emergency Department ICU
8.3 Other publications

1. Büki, A ; Barzó, P ; Demeter, B ; Kanizsai, P ; Ezer, E ; Tóth, P ; Horváth, P ; Varga, C
(IF: 0.252 )

2. Varga, Csaba ; Lelovics, Zsuzsanna ; Soós, Viktor ; Oláh, Tibor
(IF: 0.322)

3. Betlehem, József ; Varga, Csaba ; Berényi, Tamás ; Oláh, András

4. Radnai, Péter ; Szöts, Mónika ; Rádai, Ferenc ; Horváth, Gyula ; Varga, Csaba ; Fogas, János ; Szörényi, Péter ; Horváth, Zoltán ; Bajzik, Gábor ; Moizs, Mariann et al.
(IF: 0.376)

5. Varga, Csaba ; Nagy, Ferenc ; Drubits, Katalin ; Lelovics, Zsuzsanna ; Varga, Györfi Krisztina ; Oláh, Tibor
(IF: 0.386 )
6. **Varga, Csaba**; Orbán, Sándorné; Lelovics, Zsuzsanna; Zádori, Péter; Betlehem, József; Fülöp, Norbert; Oláh, Tibor


7. **Varga, Csaba**


**Cumulative IF: 5.078**

8.4 Other publications, other oral and poster presentations not related to the thesis

1. **Varga, Csaba**; Garábi, Beáta; Kiss, Mariann

Miért nem figyelnek a gyerekek matek órán? [Why are not the children interested in maths?]


2. **Varga, Csaba**

Hibák és szövődmények CPR kapcsán

In: László, István; Szabó, Zoltán; Fülesdi, Béla

3. Doloczki, Örs; Koch, Márton; Varga, Csaba

**Sepsis 6 protokoll adaptálása a SMKMOK Sürgősségi Betegellátó Centrumában**


4. **Varga, Csaba**

**Tromboembóliák, antikoagulálás, sürgősségi ellátás pp. 22-22., 1 p.**

In: Betlehem, József; Radnai, Balázs; Deutsch, Krisztina; Bánfai, Bálint; Pandur, Attila; Schiszler, Bence XII. Pécsi Sürgősségi Napok: XII. Critical Care Days in Pécs: előadáskivonatok, absztrakto. Pécs, Magyarország : Pécsi Tudományegyetem Egészségtudományi Kar (PTE ETK), (2017) p. 47

5. **Varga, Csaba**; Tóth, Kálmán ; Sánta, Lajos

**Doktor úr, szorít a mellkasom, mintha abroncs lenne rajta!**

In: Magyar, Sürgősségi Orvostani Társaság 5. Fehérvári Atherosclerosis Találkozó
Budapest, Magyarország (2017) p. online

6. **Varga, Csaba**

**Gondolatok a sürgősségi ellátás finanszírozásáról**


7. **Varga, Csaba**; Kiss, Mariann ; Soós, Viktor ; Lelovics, Zsuzsanna

**Multidiszciplináris sürgősségi osztályon megjelenő gyermekek epidemiológiai adatainak elemzése.**

8. **Varga, Csaba**

*A kiterjesztett okleveles ápolói szerepkörök helye a hazai sürgősségi ellátásban*

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EREDETISÉGÉRŐL

Alulírott
név: **dr. Varga Csaba**
születési név: **Varga Csaba**
anyja neve: **Vida Teréz**
születési hely, idő: **Marcali, 1966.08.31.**

Diagnostic Challenges in the Emergency Setting
című doktori értekezésemet a mai napon benyújtom a(z)
Doktori Iskola

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