Editing English texts authored by non-native speakers
Master Class
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Using Word's Track Change function we shall be 'micro-editing' a text originating from a non-native speaker during the Master Class. You will be assigned to a group of 3 and will be supported by experienced editors. A master class is, by its very nature, interactive so your active participation in the discussion is expected. In order to prepare you for this task, the pre-workshop assignment is to familiarize yourself with the text below.

If you wish to start editing the text electronically using Track Changes, please do. It would be helpful if some of you could bring a laptop with you to the session. If you are able to bring a laptop, loaded with this text and preferably with a power supply or well charged for a 3 hour session, could you please let me know at rcb@clinwrite.com.

Thanks

Pitfalls in treating severe metabolic acidosis caused by biguanides

1 Case description

We report a 72 year old male patient with known diabetes mellitus type II. He is in good general health conditions. No diabetes related end organ damages have been reported so far. Diabetes therapy has been designed by an endocrinologist at the nearby community hospital and is controled by a family practitioner regularly. The glycemia control is obtained by .... and 1000 mg metformin daily. After several days of gastroenteritis with profuse diarrhea, he reported s low back pain, thoracic opression, nausea, vomiting and weakness. Diuresis steadily declreases. His family practitioner decides to admit the patient to the next community hospital with a suspicion of myocardial infarction or aortic dissection. The patient has then been transfered to our emergency department after the detection of severe kidney failure, hyperkalemia and massive lactic acidosis.

At admission, he is aggitated, has elevated respiratory rate and shows deep breathing with obvious active expiration. The blood pressure is 65 to 30 mmHg and heart rate is 74/Min. The limbs are cold, but no skin mottling is present. The abdomen is without attracting attention. The ECG shows a right bundle branch block (RBB) and a first degree atrio-ventricular block. An ultrasound investigation demonstrates no pathologic findings of the thoracic and abdominal organs. The right and left ventricle have good contrac- tility without any regional dysfunction. The evaluation of fluid status by the diameter of the inferior vena cava is difficult by reason of the respiratory abdominal wall move- ments. The laboratory values are as follows: paO_2=13.0 kPa, $paCO_2$ = 2.2*kPa*, pH=6.64, $[HCO^-]$=1.7 mmol/L], Lactate= 15 mmol/L, $[Na^+]$=134 mmol/L, $[K^+]$=7.1 mmol/L,

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[Cl^-]=105 mmol/L, Hb=13.2 g/dL, Lc=23.5 K/μL, Tc=477 K/μL, CRP 68 mg/L, Creati- nine 1665 μmol/L. Two blood cultures are sampled and broad spectrum antibiotic therapie has been started. A consecutive neurologic deterioration and increase of the lactate concen- tration is observed during the evaluation in the emergency department, despite immediate treatment of the hypovolemia and the metabolic acidosis with fluid and sodium bicarbonate.

We retained the following main problems:

- severe lactic and hyperchloremic acidosis triggered by biguanides and acute kidney failure (MALA)
- circulatory shock, probably caused by the biguanide effect or the severe acidosis
- acute kidney failure (KDIGO 3) caused initially by dehydration and followed by shock
- Hyperkalemia

The patient is transfered to the ICU with diagnosis of severe metformin induced acidosis (MALA). Increasing the sodium value from 134 mmol/L to 146 mmol/L with sodium bicarbonate 8.4% permits to ameliorate pH from 6.6 to 7.08, while the patient keeps maximal respiratory compensation with arterial pCO_2 of 1,3 kPa (3.7 mmHg). Because the neurological status worsen steadily, we decide to intubate. In order to preserve spontaneous breathing and respiratory compensation, we performe fiberoptic oral intubation with only minor sedation and local anesthesia of the oropharynx and the larynx. The patient maintaines spontaneous breathing at the ventilator and we observe a respiratory volume of 30 L/Min and a tidal volume of 1'346 mL (Fig. 1 auf der n¨achsten Seite). Respiratory compensation of the severe metabolic acidosis is preserved over several hours, without signs of any respiratory fatigue. A Swan-Ganz catheter was introduced, which demonstrates a cardiac output of over 10 L/min, $S\bar{v}O_2$ 86%, a PAOP of 10 mmHg and a diastolic pulmonary artery pressure of 18 mmHg. This excludes low oxygen transport as a contributor of lactic acidosis. However, arterial blood pressure doesn't increase, despite volume resucitation and norepinephrine application. Because of severe hypotension, continuous renal replacement therapy (CRRT) with hemodiafiltration rather than intermittent dialysis is started to eliminate metformin, to correct the elevated potassium values and to treat uremia [2, 3, 4]. We use elevated continuous dialysis doses to facilitate biguanide elimination. After starting

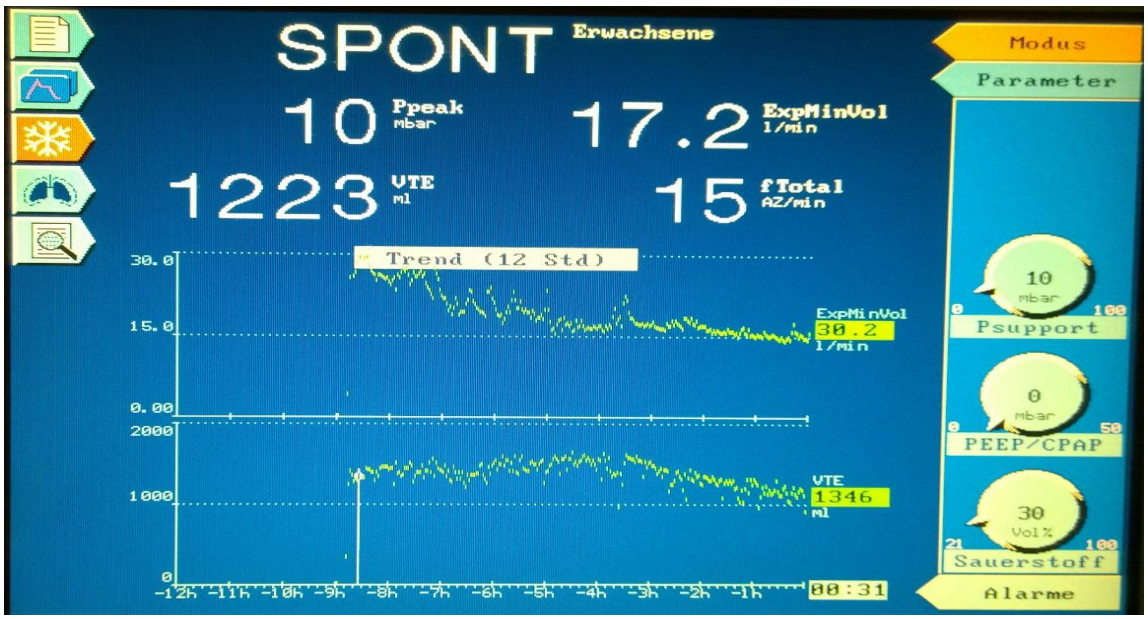

Abbildung 1: Evaluation of minute ventilation

CRRT, we observe a rapid decrease in the strong ion difference (SID) associated with a transient worsening of the metabolic acidosis (Fig. 2 auf der nächsten Seite). A continuous lactate reduction with a consecutive increase of the SID and pH could be observed only some hours after the start of CRRT. We observe a stabilization of the circulation and disappearance of the RBB. The patient has been extubated 24 h later despite a moderate delirium. Renal function is steadily recovering and antibiotic treatment has been stoped when blood cultures results return negatives.

2 Comment

Biguanides are used frequently in type two diabetic patients. Metformin improves glucose control and long term outcome, especially in obese patients. Metformin is excreted unchan- ged by the kidneys throug glomerular filtration and possibly through tubular secretion. Metformin inhibits the redox shuttle enzyme mitochondrial glycerolphosphate dehydro- genase (mGPD), resulting in a reduced conversion of lactate and glycerol to glucose [1]. Especially when metformin is overdosed or renal elimination is reduced, severe metformin associated lactic acidosis (MALA) may occur [5]. Our patient has an acute kidney injury from dehydration caused by persisting vomiting and diarrhea over several days. This symptoms may have been caused mostly by the continuous intake of metformin, but may be agravated through a combination of severe acidosis and renal failure. The prognosis of

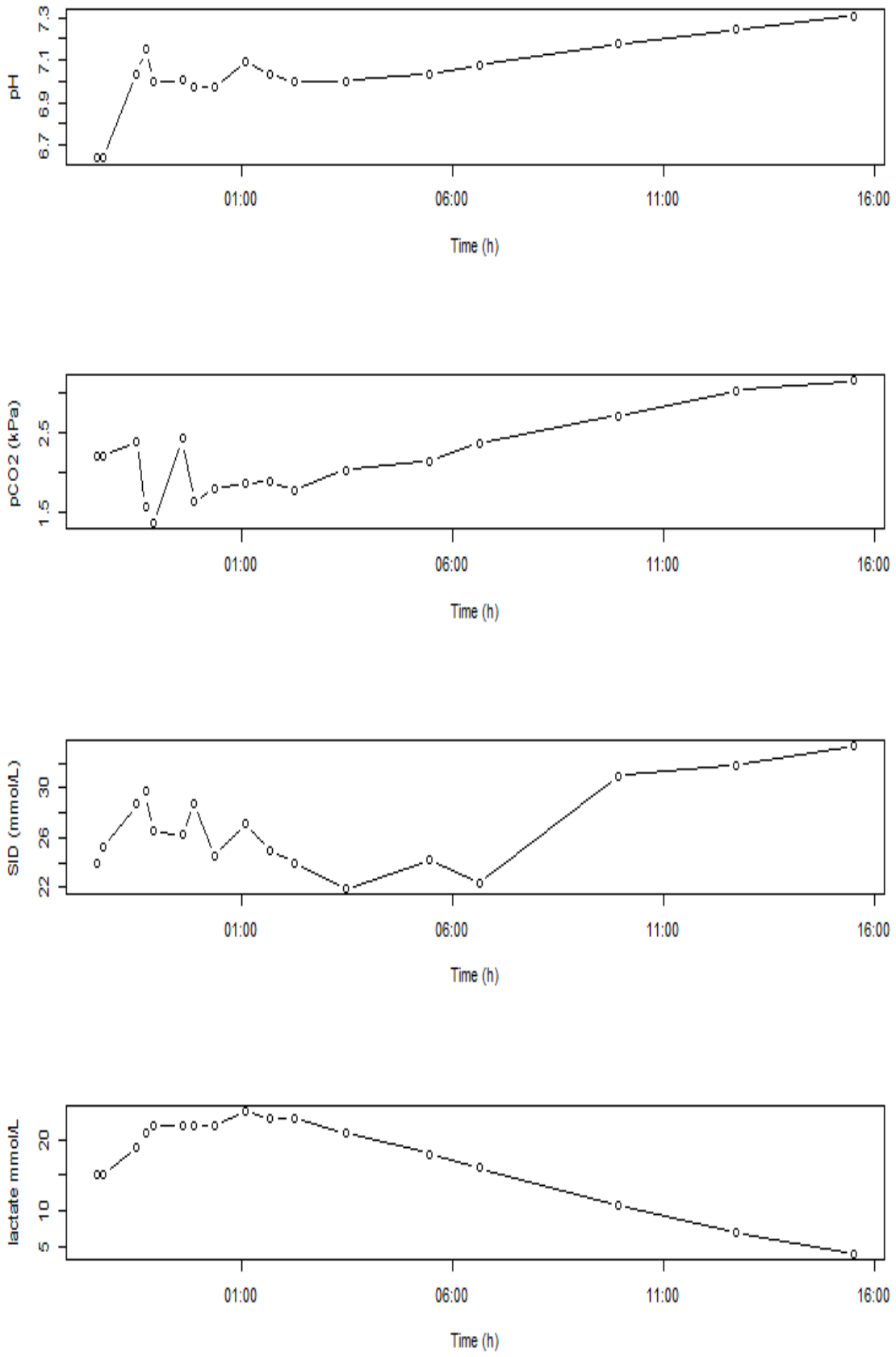

Abbildung 2: Effect of hemodiafiltration on the SID

MALA is not directly related to the severity of metabolic acidosis or lactate level, but to the development of multiorgan failure [6, 7, 8]. Despite the fact, that the outcome of metformin associated lactic acidosis is better than the outcome of severe lactic acidosis of other origin [9], mortality is between 25 and 50 % [10, 11]. Treatment of MALA is challanging and contains several pitfalls.

The principal point of treatment [10] is a reduction of metformin levels by dialysis, especially when the patient is in acute kidney failure. Dialysis is effective, because metformin is highly water soluble, minimally protein bound and has a molecular weight less than 500 D [5, 4]. However, installation of dialysis is a complex procedure requiring a specialized team and introduction of a vascular access. This is especially difficult in delirious, aggitated and hemodynamically instable patients. Therefore, supportive therapy in an ICU is of key importance. The main goal of supportive care are the amelioration of the severe metabolic acidosis, hemodynamic stabilization and preventing further complications, e.g. aspiration. The most important physiologic mechanism to compensate for severe metabolic, especially lactic acidosis is hyperventilation. Minute ventilation can be increased to more than 30 L/Min, with a considerable decrease of the pCO_2 level. The later can be as low as 1 kPa. Often, patients with MALA have to be intubated because of neurologic deterioration, including coma or severe aggitation, to perform diagnostic tests or to introduce vascular accesses. Standard intubation procedure requieres induction of general anesthesia with muscle relaxation followed by controlled mechanical ventilation. Controlled mechanical hyperventilation is not possible to the same level as the spontaneous ventilation. Thus, intubation and mechanical ventilation may provoke an immediate and severe decrease in pH. Further, positive pressure and the effect of general anesthesia can aggravate hypotension and shock, often low responsive on vasopressor application due to the severe acidosis. We therefore propose fiberoptic intubation under light sedation and topic anesthesia of the pharyngeal mucosa, followed by immediate pressure support ventilation (PSV). This approach allow maintaining a maximum of respiratory compensation, even during prolonged time.

A second problem can occur after the start of renal replacement therapy. Often, the initial intervention in severe metabolic acidosis is the application of 8,4% sodium bicarbonate. This intervention increases the strong ion difference (SID) according to the Stewarts acid-base theory by increasing $[Na^+]$ in the extracellular space [12, 13]. Renal replacement therapy however, is rapidly adjusting the elevated $[Na^+]$ values, and thus decreasing SID. Therefore, metabolic acidosis can deteriorate at in the early phase of renal replacement therapy. The effect of dialysis on acidosis usually can be observed after a delay of some hours caused to a decrease of lactate levels.

A third problem is the lactic acidosis by itself. In patients with MALA, severe hypotension and shock is often present. Therefore, investigations to find alternative reasons for shock, especially cardiogenic shock or intercurrent septic shock must be performed. We propose transthoracic echocardiography and procurement of blood cultures. Invasive hemodynamic monitoring is warranted in severe cases and initiation of antimicrobial treatment should be started early, while waiting blood culture results.