Hypocapnia and mental stress can trigger vicious circles in critically ill patients due to energy imbalance: a hypothesis presented through cardiogenic pulmonary oedema

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The pathophysiologic significance of hypocapnia is strongly underestimated both in functional and organic diseases. Alterations of carbon dioxide levels immediately appear in the cytoplasm, causing abrupt pH changes. Compensatory mechanisms develop with latency, so intracellular alkalosis or acidosis can affect metabolism for hours/days. Hyperventilation alkalosis increases metabolic energy/O_2 demand, while ATP production is often reduced due to developing hypophosphatemia. A healthy organism serves the increased energy demand conveniently, as a consequence, the excitability of the corticospinal and neuromuscular systems grows. Functional diseases can occur due to increased membrane Ca^{2+} transients but tissues remain structurally unchanged. By contrast, a critically ill myocardium cannot satisfy the increased energy demand caused by acute hypocapnia. Vicious circles can occur, with cardiac forward and backward failure; pulmonary wedge pressure increases parallel with the lack of energy which can lead to pulmonary oedema and death. Hypocapnia can generate fatal vicious circles in several critical illnesses. Sympathicotonia and hypocapnia enhance arousal and make biological systems energetically unstable, thus vicious circles almost unavoidably occur. Somatic and psychic processes mutually influence each other, resulting in psychosomatic or somatopsychic disorders. The ability to provide energy supplies can be an important dividing line between organic and functional diseases.

(Neuropsychopharmacol Hung 2018; 20(2): 65–74)

Keywords: cardiogenic pulmonary oedema, energy-demand, hypocapnia, psychosomatic pathomechanism, vicious circle

INTRODUCTION

The physiological and pathophysiological effects of carbon dioxide are underrepresented and underestimated in the literature, including cardiology. Recent research also confirms the old sentence that "biological membranes do not represent a barrier to CO_2 transport" (Missner et al. 2008). Alterations of carbon dioxide levels change the extracellular and intracellular H^+ concentrations very quickly and efficiently, which can only be normalized after 1-120 hours by compensatory mechanisms. However, changes in acidity have extraordinary importance (Relman 1972): "By affecting the charge on proteins (enzymes) and other critical reactive groups, pH influences the rates of metabolic reactions, the binding of molecules, the actions and distribution of drugs and so forth." That is why the homeostasis of the body treats the preservation and restoration of physiological intracellular and extracellular pH as a priority task. Logically, restoring only the original conditions can be perfect for pH reinstatement, in all other cases, dysregulation and metabolic remodelling can develop – by the ripple effect (Sikter et al. 2017b). Alterations of intracellular acidity change metabolism basically, in many ways not yet clarified; alkalosis usually causes acceleration while acidosis slows it down. As a result, ATP demand also increases or decreases. A sympathicotonia-like condition develops during alkalosis while acidosis changes the metabolism towards hibernation. In alkalosis (such as acute hypocapnia), the reaction of an organism depends substan-

tially on its ability to mobilize enough ATP energy. In a young, healthy body, ATP production is tailored to the requirements, but the increased corticospinal (Hartley et al. 2016) and neuromuscular excitability (increased arousal) is often associated with hyperventilation/hypocapnia, and symptoms of functional disorders also frequently develop (Gardner 1996). In contrast, a critically ill patient or diseased tissue (such as a sick myocardium) is unable to adapt to the increased demand for ATP production (Orchard and Kentish 1990). Vicious circles can develop, where the causative element (in this case the hypocapnia), it is not only a consequence but also a cause of the progression, so that a deadly spiral can occur (Sikter et al. 2017b). Acidosis is the contrast to alkalosis: it slows down the enzymatic and membrane processes saving energy. That can be useful (life-saving) in the short term (Laffey and Kavanagh 1999), but in the long run, both chronic hypocapnia and chronic hypercapnia will lead to metabolic remodelling and diseases. (Therefore, the tacitly accepted work hypothesis that compensated chronic hypocapnia or hypercapnia is tolerable and harmless is not true.) Sick, dysfunctional cells and tissues have reduced ATP production which is also characteristic of heart diseases. It is not a coincidence but a law that vicious circles are formed in living organisms, especially in cases of severe hyperacute illnesses. The living organism/cell is highly structured; it is at an energetically much higher level than its inanimate environment. Therefore, if the measure of instability is high, the equalization of energy levels will be fast, like an avalanche, self-reinforcing vicious circles will occur. We have to consciously seek the exact pathophysiology of these so we can interrupt the downward spiral, so that an upward recovery could develop (a virtuous cycle).

INTRACELLULAR ALKALOSIS INCREASES METABOLISM: GROWTH IN O_2 CONSUMPTION, ATP DEMAND AND PRODUCTION

Alterations of carbon dioxide level change intracellular H^+ concentration so rapidly that no compensatory mechanism could follow it. In the case of acute hypocapnia, formatting of lactate is compensatory. However, at least one hour is needed for the development of the steady state (Petroff et al. 1985). After the development of acute hypocapnia or hypercapnia, the restoration of the original intracellular pH (the steady state) requires hours by transporting H^+ through membranes, and 5-7 days by changing HCO_3^- concentration through renal metabolic compensation (Gennari et al. 1972). Furthermore, if the pCO_2 level continually decreases, the steady state cannot develop at all. On the other hand, these compensatory processes also slow down the recovery of the original state; the hyperventilation alkalosis may transform into metabolic acidosis either temporarily or permanently. The function of many enzymes changes in alkalosis because virtually all enzymes have a well-defined pH optimum (Relman 1972). For example, lactate production increases both during aerobic and anaerobic glycolysis and it burns aerobically at the end. Cytoplasmic alkalosis enhances both passive and active transport of ions, especially of Ca^{2+} (Orchard and Kentish 1990, John et al. 2018). Overall, cytoplasmic alkalosis (e.g. during acute hypocapnia) leads to an increase in oxygen consumption, as well as CO_2 and ATP output (up to 20%) (Khambatta and Sullivan 1974). The increased metabolic expenditure could not originate alone from the raised work of breathing (Otis 1954) because the hyperventilation was passive during the study.

It is a fundamental principle that the healthy cellular activity adapts to energy needs and regulation maintains constant levels of cytoplasmic ATP concentration (Das 2003). On the other hand, the energy-homeostatic function of aging, sick cells deteriorates e.g. in the myocardium (Orchard and Kentish 1990, Das 2003, Cha et al. 2003). In the case of increased energy demand, creatine phosphate concentration decreases initially in the diseased heart muscle, which is a mobilizable energy reserve (Neumann et al. 2003). In a typical case, the relaxation function of the myocardium will deteriorate first (Zile et al. 2004). Some authors found an inverse relationship between relaxation and diastolic cytoplasmic Ca^{2+} concentration in the myocardium (Stern et al. 1988) since Ca^{2+} extrusion decreases from cytosol in case of ATP deficiency (Noble and Herchuetz 2007). That is, myocardial relaxation function is highly susceptible to ATP depletion (Ha and Oh 2009). Increased stiffness and relaxation failure of myocardium raises pulmonary wedge pressure (PWP) (Paintal 1969). The excitement of pulmonary stretch receptors results in dyspnoea (Mauck et al. 1964) and hyperventilation/hypocapnia. In this regard, pulmonary stretch J receptors cooperate with central respiratory receptors (Solin et al. 1999). In chronic congestive heart failure hypoxia may also contribute to the development of hypocapnia (Fanfulla et al. 1998), Cheyne-Stokes Respiration (CSR), although others exclude this pathophysiological factor (Yamashiro and Kryger 1993).

CRITICAL HEART FAILURE CANNOT WITHSTAND THE INCREASED LOAD, VICIOUS CIRCLES DEVELOP

It is a fact that efficiency of heart function is significantly deteriorated in decompensated heart failure; both heart muscle and the whole body increase oxygen consumption compared to healthy control and so far there is no acceptable explanation for this (Zhang et al. 2015). There is a significant inverse relationship between cardiac output and peak O_2 consumption as determined during exercise test of compensated cardiac patients (Matsumoto et al. 2000, Arena et al. 2007, Arena et al. 2008). A correlation was also confirmed between cardiac output in heart failure and $PETCO_2$ (Arena et al. 2008). In case of a healthy myocardium during exercise, $PETCO_2$ does not decrease but slightly increases. There is an inverse correlation between the decreasing $PETCO_2$ and PWP during rest (Olson et al. 2007) or exercise; the left ventricular end-diastolic pressure and PWP rise are considered to be a symptom of increased left ventricular stiffness, i.e., a sign of heart failure. Numerous studies address this issue, as to reduce pulmonary wedge pressure is a new therapeutic goal (Guazzi et al. 2011).

Chronic congestive heart failure is commonly associated with spontaneous Cheyne-Stokes Respiration (CSR, synonyms are: central sleep apnea, oscillatory breathing, periodic breathing), which is a crescendo-decrescendo hyperpnoea followed by a short period of hypopnea/apnea. Overall, hypocapnia dominates, which is also reflected in a negative sum of base excess. CSR occurs in 8-50% of chronic heart failure patients (Ingbir et al. 2002); it is a poor prognostic sign of disease outcome (Lanfranchi et al. 1999). (CSR should not be confused with obstructive sleep apnea, in the former hypocapnia dominates, while in the latter hypercapnia, Sikter et al. 2017b).

In case of a healthy myocardium, stroke volume and instantaneous $PETCO_2$ oscillate together (Davies et al. 2000). In contrast, in case of severe cardiac patients (waiting for heart transplantation and showing periodic breathing at rest), a correlation between the measure of breathing oscillation and PWP was reported (Corrá et al. 2002). Developing hypocapnia (CSR) during chronic congestive heart failure is a sign of worsening because it reflects the approaching exhaustion of the heart's reserve energy.

The sick myocardium has a worsened relaxation ability, thus the diastolic pressure of the heart rises, resulting in increased PWP and hyperventilation/hypocapnia. Decreasing CO_2 levels in different tissues and heart muscle increase O_2 consumption and energy demand; the sick heart muscle cannot satisfy the need, ATP concentration of tissues begins to drop, myocardium stiffness increases, cardiac output decreases. The respiratory centre in medulla oblongata periodically restores normal pCO_2 level initially (CSR). Then, the periodic apnea and oscillation of breathing disappear, continuous, increasing hyperventilation and decreasing pCO_2 develops. When the compensatory ability of the apnea centre ceases, pulmonary oedema may occur, which is often fatal.

Capacity for ATP production and myocardial relaxation in this connection gradually decreases in the aging, sick heart muscle cells, which at a certain point leads to the elevation of left ventricular end-diastolic and consequently of the PWP. (Initially, this would develop only during exercise load). PWP elevation increases breathing rate and tidal volume through J receptors, resulting in hypocapnia, which increases O_2 consumption and ATP demand both in the myocardium and body tissues. In case of ATP deficiency, the diastolic Ca^{2+} concentration of the heart muscle increases continuously; myocytes can relax even less, the PWP rises further, and so forth. (Initially, the respiratory center normalizes CO_2 level periodically, then it also becomes exhausted and a vicious circle develops.)

HOW COULD WE BREAK OFF THE VICIOUS CIRCLE GENERATED BY HYPOCAPNIA IN DECOMPENSATED CONGESTIVE HEART FAILURE?

One of the theoretical options is to raise arterial pCO_2 level to the normal range. During CSR, hypocapnia causes compensatory apnea and periodicity of breathing, as it was demonstrated by the continuous administration of a low concentration of CO_2. However, the continuous administration of CO_2 may have inverse effects (Lorenzi-Filho et al. 1999). Low-dose carbon dioxide applied only during hyperventilation phases almost abolished pCO_2 level oscillations (Giannoni et al. 2010). It is assumed by the authors that dynamic CO_2 therapy can decrease elevated PWP levels, however, it was not studied. According to another study, low dose CO_2 administered at a mathematically calculated time during CSR minimized the oscillation of carbon dioxide level, and it certainly had many beneficial effects (Mebrate et al. 2009). One of the highlighted effects of dynamic CO_2 therapy is that it eliminates the hypocapnia-induced sympathicotonia-like condition which occasionally occurs not only due

to CSR but also to continuous CO_2 administration because of counter-regulatory effects. Namely, during CSR a sympathetic overactivation occurs (Lorenzi-Filho et al. 1999, Mansfield et al. 2003, Mebrate et al. 2009). These facts well suit the hypocapnia-induced increased metabolism model hypothesized by the author (Sikter et al. 2017a), although the acute hypocapnia-induced state only imitates sympathicotonia, and differ terminologically from each other. The direct reduction of PWP is another possibility to interrupt the vicious circles. Using nitroprusside infusion has a rather theoretical significance (Olson et al. 2007), while sildenafil is a very promising drug in the treatment of chronic congestive heart failure (Guazzi et al. 2011).

It appears that cardiogenic pulmonary oedema has at least two forms. In addition to classical "asthma cardiale", where hyperventilation/hypocapnia plays an important role, a hypercapnic form also exists which occurs only with severe hypercapnia, while normocapnia has a protective effect (Contou et al. 2015). The pathophysiology of the two types should be different. According to Valipour (Valipour et al. 2004), non-invasive pressure support ventilation often alleviated respiratory distress in severe acute cardiogenic pulmonary oedema except in patients with hypocapnia, who had a poor prognosis.

While previously morphine was the first choice of drugs for acute cardiogenic pulmonary oedema, its application had been significantly reduced due to its many side effects (Purvey et al. 2017, Bosomworth 2008). The main, often fatal adverse effect of morphine is respiratory depression. According to the author respiratory depletion is the primary (and not an adverse) effect of morphine in hypocapnia-related cardiogenic pulmonary oedema. Morphine is able to interrupt the vicious circle of hyperventilation/hypocapnia, and in this way reduce PWP, and eliminate pulmonary oedema. Morphine should only be administered in hypocapnia cases, very carefully (in small doses or slow infusion), and monitoring of $PETCO_2$ is also recommended. In such cases morphine will get back its old authority. On the other hand, it is necessary to look for similar agents, whose effects can be more easily calculated.

Several lines of data indicate that hypocapnia plays a pathophysiological role not only in cardiac backward but forward failure (Wahba et al. 1996, Matsumoto et al. 2000), even in circulatory shock (Jin et al. 2000). Many things suggest that hypocapnia can exert a pathogenic effect in some of the critical illnesses. Increased O_2 and energy demand may be present in the background and thus generate vicious circles. Laffey and Kavanagh (Laffey and Kavanagh, 1999; 2002) suggested that the severely damaging effect of hypocapnia is almost independent of the underlying illness; the critical condition is what is decisive. Laffey (Laffey et al. 2000) mostly dealt with ARDS, introducing the concept of permissive hypercapnia, which may have a protective effect on a variety of hyperacute diseases in the short-term – as opposed to hypocapnia. For example, hypocapnia may also have a pathogenetic role in septic shock (Mallat et al. 2017). Hypocapnia is a very bad prognostic sign also in acute stroke, which cannot be a simple coincidence (Plum 1972, Laffey and Kavanagh, 1999).

LEVELS OF AROUSAL AND ENERGY DEMAND CORRELATE WITH INTRACELLULAR pH

Enhanced arousal is closely related to hyperventilation alkalosis and/or activation of the sympathetic nervous system (SNS) (Sikter et al. 2009). Both of them cause intracellular alkalosis in the affected organs/cells. Both of them take part in life stress (Sikter et al. 2017a), and in respiratory panic disorder (PD) (Sikter et al. 2007; 2009). It is beneficial to compare the two main arousal-increasing factors: effects of catecholamines and acute hypocapnia. (Table 1.)

SNS induced alterations (e.g. in obesity) are excessively regional specific and inconsistent (Davy et al. 2009), they may be consequences of hormonal contra- and dysregulation (Sikter et al. 2017a). This thesis cannot be proven these days since real-time, synchronized monitoring of all hormones is not available yet. In contrast, the distribution of hypocapnia (and pCO_2) is relatively consistent in the cytoplasm of tissues - except the differences in the arteriovenous ends of the capillaries. Of course, compensatory remodelling of intracellular pH also develops in chronic hypocapnia due to hormonal/humoral mechanisms (Sikter et al. 2017a). Both catecholamines (Monroe et al. 2001) and hypocapnia (see above) increase metabolism, energy demand and enhance arousal. Beta-adrenergic blockade significantly inhibits resting energy expenditure (induced by sympathicotonia) and decreases arousal (Chamberlain et al. 2006). Acute hypocapnia affects the central nervous system similarly as SNS, but there are also many differences. There is not enough physiological and pathophysiological data to understand the exact role of hypocapnia and to use it for intervention. Namely, in the literature, several effects were considered to be of the SNS which, in fact, were

Table 1. Similarities and differences between arousal enhancing factors

	Catecholamines	Hypocapnia
Arousal	increases	increases
Membrane ion permeability (e.g. Ca^{2+})	increases	increases
O_2 consumption, metabolism	increased	increased
Resting energy expenditure (REE)	increases, organ specific, attenuated with aging, obesity, etc. (Bell et al. 2001)	increases
Tissular sensitivity	there are extreme differences among organs (Davy et al. 2009); (different number of receptors and SNS distribution) **Is it a hormonal/metabolic dysregulation?**	there is no "CO_2 membrane-receptor"; the distribution is homogenous
Effect of beta-adrenerg blockage on the REE	decreases the pH in the affected cells, decreases REE and metabolism	not known (it is expected to be ineffective)
Effect on heart rate	increases	increases
Effect on cardiac contractility	increases	? (maybe increases)
Effect of normocapnia	starting position	it nullifies the effect
	They increase each other's effectivity; they are synergists	

direct consequences of decreased carbon dioxide levels. Their assumed common point of attack is to influence of intracellular pH.

EMOTIONS CAN INFLUENCE THE COURSE OF SOMATIC DISEASES CONNECTED TO AROUSAL

It is known that emotions can affect organic diseases in favourable or unfavourable directions, they can increase or decrease ventilation inducing hypo- or hypercapnia (Van Diest et al. 2006). Tully (Tully et al. 2015) wrote that "although anxiety has been clinically linked with CAD for more than 100 years (…), the nexus between PD and CAD remains tenuous(…)". PD and major depression are the two extreme poles of arousal; we can consider the pathophysiology of respiratory panic disorder as a manifestation of hyperarousal (Sikter et al. 2017b). We should negotiate separately about hyper- and hypoarousal from the pathophysiological point of view despite the fact that they can switch each other.

Some studies have found a clear correlation between PD and risk of acute cardiovascular mortality (Coryell et al. 1986, Eaker et al. 2005, Albert et al, 2005). Anxiety increased the risk of sudden cardiac death and a fatal CAD but not of chronic CAD events. In contrast, according to a large cohort study (Walters et al. 2008), new panic attacks under the age of 50 increase the crude risk of AMI. The authors postulated that PD was often a misdiagnosis instead of CAD in early cases. A recent, more accurate meta-analysis (Tully et al. 2015) found that PD is a risk factor for AMI and other major adverse cardiac events, but there is only low-quality evidence for the association between PD and CAD. There is also an uncertainty in the cause-effect relationship, reverse causality cannot be ruled out.

Panic attack (hyperarousal) cannot cause AMI or sudden death in healthy humans; it needs a co-existing CAD (which is often hidden) or metabolic disorder (e.g., variant angina). Fleet (Fleet et al. 2005) reported that panic attacks induced significant perfusion shortages in patients who had CAD and PD at the same time (Fleet et al. 2005). In most cases, the pathomechanism has an ischemic background, that is why the O_2/energy demand and O_2/energy supply imbalance has a determining role (Blumenthal et al. 1995, Soares-Filho et al. 2012). According to our hypothesis, it is essential that hyperventilation alkalosis (and also catecholamines) itself increases O_2/energy demand (see above). On the other hand, hypophosphatemia caused by acute hypocapnia (Brautbar et al.1985) is a hazard to ATP-energy supply (Keskek et al. 2015). This may be a newly discovered vicious circle.

"Variant angina" described by Prinzmetal (Prinzmetal et al. 1959) has been already exceeded by the theory of coronary artery vasospasm which is a much

broader concept (Yasue et al. 2008). Its prevalence is very high, although not exactly known. In Japan, the prevalence of coronary artery vasospasm happens in up to 40% of patients who underwent coronary arteriography. It is estimated to be lower in the west (4-12%). Coronary artery vasospasm has a similar significance as the arteriosclerotic CAD. Briefly, a significant proportion of middle-aged people suffer from coronary artery vasospasm which can develop with or without coronary atherosclerosis. Precipitating factors are acute hyperventilation, mental stress, and a dozen of pharmacological agents, e.g., catecholamines, acetylcholine, beta-adrenergic blockage. Hyperventilation seems to be a crucial triggering factor (Nakao et al. 1997). The endothelium and smooth muscle cells of coronary arteries are damaged. The exact mechanism is not known, a chronic low-grade inflammation is often present. Hypercontractility of the coronary smooth muscle is a constant symptom and mechanism. Alkalosis increases contractility due to raised cytosolic Ca^{2+} influx, (Soares-Filho et al. 2012), however, relaxation cannot develop because of decreased ATP supply (see above). Coronary artery spasm (with or without coronary atherosclerosis) can produce acute coronary syndrome and AMI. However, Ca^{2+} channel blockers have a beneficial effect on coronary spasm. Long-term survival of patients suffering from coronary artery vasospasm is usually better than from the CAD if they are treated correctly and avoid smoking.

It was stated by Huffman (Huffman et al. 2002) that sudden death is 2-4 times more common in PD than without it. Hyperventilation hypocapnia can provoke malignant cardiac arrhythmias and conduction defects with sudden death which is more frequent together with coronary artery spasm (Nakao et al. 1997), but other mechanisms are also possible. (E.g. with genetically coded disorders.)

In summary, there is no evidence that disorders with increased arousal (e.g., PD) cause atherosclerosis or other somatic disorders, but they can trigger the development of AMI and sudden death (major adverse cardiac events). Similarly, disorders with increased arousal can also influence other organic diseases in the unfavourable direction due to increased metabolic rate and decreased ATP supply. In contrast, disorders with decreased arousal (major depression) save energy in the short run but they promote the metabolic remodelling and development of somatic diseases in the long run (Sikter et al. 2017b). It is difficult to prove this hypothesis since hypoarousal and hyperarousal often switch into one another.

EPILOGUE

In the case of respiratory PD existence of vicious circles involving mental and behavioural elements was previously hypothesized (Fava and Morton, 2009).

This review presents how hypocapnia can alter and intensify metabolism through intracellular alkalosis which can trigger the different vicious circles: with rising PWP leading to lung oedema, etc. Acute hypocapnia can endanger critically ill cells/organs/organisms due to increasing energy/O_2 demand and lead to fatal outcomes. According to another mechanism, hypophosphatemia – induced by acute hyperventilation – often results in ATP deficiency which can also perpetuate vicious circles and decrease energy supply (This topic would deserve a separate review. See above.)

Vicious circles could also develop separately, although somatic and mental processes usually affect each other. The study of Walters (Walters et al. 2008) demonstrated that panic disorder can also start due to true anginas mistakenly diagnosed as PD. On the other hand PD is undoubtedly a risk factor for acute coronary events and sudden death (Tully et al. 2015). Mental disorders can worsen the somatic state of cells/organs if they are critically ill.

Hypocapnia immediately reaches every cell interior and changes (accelerates) their metabolism without delay. In contrast, neuro-humoral regulation partly depends on the neuronal pathways, and partly on the regulation of membrane receptors. Briefly, the former is a non-specific, while the latter is a targeted effect. In the first few hours of acute hypocapnia, each cell has to fight alone against increased energy demand (and possibly reduced energy supply) which is usually not difficult for a young, healthy organism. We call the least resistant places "locus minoris resistentiae". Their metabolism had been injured, congenitally or acquired. If the coronary endothelium and smooth muscle are the locus minoris resistentiae, the mental stress or hyperventilation may precipitate its spasm. If the minor resistance place is in the muscle of left heart side, a backward failure (pulmonary hypertension, congestion or oedema), and/or a forward failure (low cardiac output) will develop.

After central neurological insults (Baumann et al., 2007) pulmonary oedema and acute cardiac decompensation often occur, even in the absence of previously described heart illness. "Neurogenic myocardial injury" is a misleading diagnosis. The pathomechanism has not been clarified (Baumann et al. 2007). It seems that some brain damage generates vicious

circles through hyperventilation, which decompensate cardiac function in a short time (Williamson et al. 2015). More than a dozen central nervous system diseases and injuries (Baumann et al. 2007) often lead to death with symptoms of typical cardiorespiratory insufficiency. This mechanism could also explain why cardiac failure is the most common disease leading directly to death even among non-cardiac patients.

Delirium is common in cases of brain atrophy. Hyperventilation attacks (mental stress) most likely damage or kill the profoundly injured brain cells, so the above mentioned physiopathological mechanisms provide a clear explanation for the progression of underlying diseases during delirium (Sikter et al. 2009).

There are two possible extreme cases. It may be that only a few pacemaker cells of the heart are critically ill, and mental stress with hyperarousal causes sudden death in a young person who was otherwise healthy. According to the other extreme case, somebody has a "perfect" genome, so he/she has no locus minoris resistentiae in any vital organs, hyperarousal mental stresses do not cause sudden deterioration or damage in health, thus the person always recovers fully. On the other hand, long-lasting depression does not develop in this patient either so that he/she can live for up to 120 years and will die in marasmus.

Level of arousal, energy expenditure, and intracellular pH are related.

In summary, there seems to be a significant difference between mental and somatic diseases, namely that in the former cells/tissues/organs are sufficiently healthy to restore stress-induced injuries while the latter have less-resistance places, which cannot recover entirely. In this case, major depression would be a transition between mental and somatic diseases because repeated chronic episodes of depression may lead to progressive hippocampal atrophy (Sikter et al. 2009). Different respiratory breathing patterns, altered pCO_2 levels, constitute a critical – unexplored – chain between mental and somatic functions, affecting one another, not infrequently causing disease progression. Exploring the details would also be important because this could be a real tool in the hands of the healing physician.

CONCLUSIONS

In the case of critical illnesses, hypocapnia may lead to the fatal outcome (Laffey and Kavanagh, 1999). In the current review, that statement was presented through decompensated congestive heart failure. CO_2 has extraordinary abilities: it can cross membranes and change intracellular pH without delay. All enzymes and membrane ion-transporters have pH optima. The intracellular alkalosis mimics sympathicotonia. Hypocapnia-induced intracellular alkalosis significantly increases metabolism, O_2 demand, and it can persist for a relatively long time, primarily when a progressive, critical illness develops due to vicious circles. At the same time, the sick organism cannot meet the challenge of the increased energetic demand induced by acute hypocapnia or mental stress.

Clinicians think that hypocapnia causes harmless functional complaints, if at all. This review demonstrates that its impact could be fatal in critically ill. The turning point is whether cells/organs are able to mobilize enough ATP-energy or not.

Abbreviations:

AMI:	acute myocardial infarction
ARDS:	adult respiratory distress syndrome
ATP:	adenosine triphosphate
CAD:	coronary artery disease
Ca^{2+}:	calcium ion
CO_2:	carbon dioxide
CSR:	Cheyne-Stokes respiration
H^+:	hydrogen ion
HCO_3^- :	bicarbonate ion
O_2:	oxygen
pCO_2:	partial pressure of carbon dioxide
$PETCO_2$:	end-tidal partial pressure of carbon dioxide (in exhaled air)
PD:	panic disorder
PWP:	pulmonary wedge pressure
REE:	resting energy expenditure
SNS:	sympathetic nervous system

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REFERENCES

1. Albert CM, Chae CU, Rexrode KM et al. (2005): Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. Circulation. 111:480-7.
2. Arena R, Myers J, Hsu L et al (2007): The minute ventilation/carbon dioxide production slope is prognostically superior to the oxygen uptake efficiency slope. J Cardiac Fail. 13:462-9.
3. Arena R, Myers J, Abelia J et al. (2008): The partial pressure of resting end-tidal carbon dioxide predicts major cardiac events in patients with systolic heart failure. Am Heart J. 156:982-8.
4. Baumann A, Audibert G, McDonnell J, Mertes PM (2007): Neurogenic pulmonary oedema. Acta Anaesth Scand. 51:447-55.
5. Bell C, Seals DR, Monroe MB, et al. (2001): Tonic sympathetic support of metabolic rate is attenuated with age, sedentary life-

style, and female sex in healthy adults. J Clin Endocrinol Metab. 86:4440-4.
6. Blumenthal JA, Jiang W, Waugh RA et al. (1995): Mental stress-induced ischemia in the laboratory and ambulatory ischemia during daily life. Circulation 92:2102-8.
7. Bosomworth J (2008): Rural treatment of acute cardiogenic pulmonary oedema: applying the evidence to achieve success with failure. Can J Rural Med. 13:121-8.
8. Brautbar N, Leibovici H, Massry SG. (1983): On the mechanism of hypophosphatemia during acute hyperventilation: evidence for increased muscle glycolysis. Miner Electrolyte Metab. 9:45-50.
9. Cha YM, Dzeja PP, Shen WK, et al. (2003): Failing atrial myocardium: energetic deficits accompany structural remodeling and electrical instability. Am J Physiol Heart Circ Physiol. 284:H1313-20.
10. Chamberlain ST, Müller U, Blackwell AD, et al. (2006): Noradrenergic modulation of working memory and emotional memory in humans. Psychopharmacology 188:397-407.
11. Contou D, Fragnoli C, Cordoba-Isquierdo A et al. (2015): Severe but not mild hypercapnia affects the outcome in patients with severe cardiogenic pulmonary edema treated by non-invasive ventilation. Ann Intensive Care 5:14
12. Corrá U, Giordano A, Bosimini E et al. (2002): Oscillatory ventilation during exercise in patients with chronic heart failure. Clinical correlates and prognostic implications. Chest 121: 1572-80.
13. Coryell W, Noyes R, House D (1986): Mortality among outpatients with anxiety disorders. Am J Psychiatry 143:508-10.
14. Das AM (2003): Regulation of the mitochondrial ATP-synthase in health and disease. Mol Genet Metab. 79:71-82.
15. Davies LC, Francis DP, Crisafulli A et al. (2000): Oscillations in stroke volume and cardiac output arising from oscillatory ventilation in humans. Exp Physiol. 85:857-62.
16. Davy KP, Orr JS (2009): Sympathetic nervous system behavior in human obesity. Neurosci Biobehav Rev. 32:116-24.
17. Eaker ED, Sullivan LM, Kelly-Hayes M et al. (2005): Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: The Framingham offspring study. Psychosom Med. 67:692-6.
18. Fanfulla F, Mortara A, Maestri R et al. (1998): The development of hyperventilation in patients with chronic heart failure and Cheyne-Stokes respiration. A possible role of chronic hypoxia. Chest. 114:1083-90.
19. Fava L, Morton J (2009): Causal modeling of panic disorder theories. Clin Psychol Rev. 29:623-37.
20. Fleet R, Lespérance F, Arsenault A et al. (2005) Myocardial perfusion study of panic attacks in patients with coronary artery disease. Am J Cardiol. 96:1064-8.
21. Gardner WON (1996): The pathophysiology of hyperventilation disorders. Chest. 109:516-34.
22. Gennari FJ, Goldstein MB and Schwartz WB (1972): The nature of the renal adaptation to chronic hypocapnia: J Clin Invest. 51:1722-30.
23. Giannoni A, Baruah R, Willson K et al (2010): Real-time dynamic carbon dioxide administration: A novel treatment strategy for stabilization of periodic breathing with potential application to central sleep apnea. JACC 56:1832-7.
24. Guazzi M, Vicenzi M, Arena R et al. (2011): Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 124:164-74.
25. Ha JW and Oh JK (2009): Therapeutic strategies for diastolic dysfunction: a clinical perspective. J Cardiovasc Ultrasound. 17:86-95.
26. Hartley GL, Watson CL, Ainslie PN et al. (2016): Corticospinal excitability is associated with hypocapnia but not changes in cerebral blood flow. J Physiol. 594:3423-37.
27. Huffman JC, Pollack MH, Stern TA (2002): Panic disorder and chest pain: Mechanisms, morbidity, and management. Primary Care Companion J Clin Psychiatry 4:54-62.
28. Ingbir M, Freimark D, Motor M et al. (2002): The incidence, pathophysiology, treatment and prognosis of Cheyne-Stokes breathing disorder in patients with congestive heart failure. Herz. 27:107-12.
29. Jin X, Weil MH, Tang W, et al. (2000): End-tidal carbon dioxide as a noninvasive indicator of cardiac index during circulatory shock. Crit Care Med. 28: 2415-9.
30. John S, Kim B, Olcese R, et al. (2018): Molecular determinants of pH regulation in the cardiac Na^+-Ca^{2+} exchanger. J Gen Physiol. 150:245-57.
31. Khambatta HJ and Sullivan SF (1974): Carbon dioxide production and washout during passive hyperventilation alkalosis. J Appl Physiol. 37:665-9.
32. Keskek SÖ, Sagliker Y, Kirim S et al. (2015): Low serum phosphorus level in Massry's phosphate depletion syndrome may be one of the causes of acute heart failure. J Nutr Sci Vitaminol (Tokyo). 61:460-4.
33. Laffey JG and Kavanagh BP (1999): Carbon dioxide in the critically ill—too little of a good thing? Lancet 354:1283-6.
34. Laffey JG and Kavanagh BP (2002): Hypocapnia. N Engl J Med. 347:43-53.
35. Laffey JG, Tanaka M, Engelberts D et al (2000): Therapeutic hypercapnia reduces pulmonary and systemic injury following In Vivo lung reperfusion. Am J Respir Crit Care Med. 162:2287-94.
36. Lanfranchi PA, Braghiroli A, Bosimini E et al. (1999): Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. Circulation. 99:1435-40.
37. Lorenzi-Filho G, Rankin F, Bies I et al. (1999): Effects of inhaled carbon dioxide and oxygen on Cheyne-Stokes respiration in patients with heart failure. Am J Respir Crit Care Med. 159:1490-8.
38. Mallat J, Mohammad U, Lemyze M et al. (2017): Acute hyperventilation increases the central venous-to-arterial PCO_2 difference in stable septic shock patients. Ann Intensive Care 7:31-9.
39. Mansfield D, Kaye DM, La Rocca HB et al. (2003): Raised sympathetic nerve activity in heart failure and central sleep apnea is due to heart failure severity. Circulation. 107:1396-1400.
40. Matsumoto, Itoh H, Eto Y et al. (2000): End-tidal CO_2 pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. JACC 36:242-9.
41. Mauck HP Jr, Shapiro W, and Patterson JL Jr (1964): Pulmonary venous (wedge) pressure: Correlation with onset and disappearance of dyspnea in acute left ventricular heart failure. Amer J Cardiol. 13:301-9.
42. Mebrate Y, Wilson K, Manisty CH et al. (2009): Dynamic CO_2 therapy in periodic breathing: a modeling study to determine optimal timing and dosage regimes. J Appl Physiol. 107:696-706.
43. Missner A, Kügler P, Saparov SM et al. (2008): Carbon dioxide transport through membranes. J Biol Chem. 283:25340-7.
44. Monroe MB, Seals DR, Shapiro LF et al. (2001): Direct evidence for tonic sympathetic support of resting metabolic rate in healthy adult humans. Am J Physiol Endocrinol Metab. 280:E740-4.
45. Nakao K, Ohgushi M, Yoshimura M et al. (1997): Hyperventilation as a specific test for diagnosis of coronary artery spasm. Am J Cardiol. 80:545-9.

46. Neumann D, Schlattner U and Wallimann T (2003): A molecular approach to the concerted action of kinases involved in energy homeostasis. Biochem Soc Trans. 31(Pt 1):169-74.
47. Noble D and Schuetz A (2007): Role of Na/Ca exchange and the plasma membrane Ca^{2+}-ATPase in cell function. Conference on Na/Ca Exchange. EMBO Rep. 8:228-32.
48. Olson TP, Frantz RP, Snyder EM et al. (2007): Effects of acute changes in pulmonary wedge pressure on periodic breathing at rest in heart failure patients. Am Heart J. 153:104.e1-104.e7
49. Orchard CH and Kentish JC (1990): Effect of changes of pH on the contractile function of cardiac muscle. Amer J Physiol. (Cell Physiol 27) 258:C967-C981.
50. Otis AB (1954): The work of breathing. Physiol Rev. 34:449-58.
51. Paintal AS (1969): Mechanism of stimulation of type J pulmonary receptors. J Physiol. 203:511-32.
52. Petroff OAC, Pritchard JW, Behar KL et al. (1985): Cerebral metabolism in hyper- and hypocarbia 31P and 1H nuclear magnetic resonance studies. Neurology. 35:1681-8.
53. Plum F (1972): Hyperpnea, hyperventilation, and brain dysfunction. Ann Intern Med. 76: 328.
54. Prinzmetal M, Kannamer R, Meriss R et al. (1959): A variant form of angina pectoris; preliminary report. Am JU Med. 27:375-88.
55. Purvey M and Allen G (2017): Managing acute pulmonary oedema. Aust Prescr. 40:59-63.
56. Relman AS (1972): Metabolic consequences of acid-base disorders. Kidney Int. 1:347-59.
57. Sikter A, Frecska E, Braun IM et al. (2007): The role of hyperventilation: hypocapnia in the pathomechanism of panic disorder. Rev Bras Psiquiatr. 29:375-9.
58. Sikter A, Faludi G, Rihmer Z (2009): The role of carbon dioxide (and intracellular pH) in the pathomechanism of several mental disorders. Are the diseases of civilization caused by learnt behaviour, not the stress itself? Neuropsychopharmacol Hung. 11:161-73.
59. Sikter A, Rihmer Z and Guevara R (2017a): New aspects in the pathomechanism of diseases of civilization, particularly psychosomatic disorders. Part 1. Theoretical background of a hypothesis. Neuropsychopharmacol Hung. 19:95-105.
60. Sikter A, Rihmer Z and Guevara R (2017b): New aspects in the pathomechanism of diseases of civilization, particularly psychosomatic disorders. Part 2. Chronic hypocapnia and hypercapnia in the medical practice. Neuropsychopharmacol Hung. 19:159-69.
61. Soares-Filho GLF, Mesquita CT, Mesquita ET et al. (2012): Panic attack triggering myocardial ischemia documented by myocardial perfusion imaging study. A case report. Int Arch Med. 5:24
62. Solin P, Bergin P, Richardson M et al. (1999): Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation. 99:1574-9.
63. Stern MD, Capogrossi MC and Laatta EG (1988): Spontaneous calcium release from the sarcoplasmic reticulum in myocardial cells: mechanisms and consequences. Cell Calcium. 9:247-256.
64. Tully PJ, Turnbull DA, Beltrame J et al. (2015): Panic disorder and incident coronary heart disease: a systematic review and meta-regression in 1 131 612 persons and 58 111 cardiac events. Psychol Med. 45:2909-20.
65. Valipour A, Cozzarini W, Burghuber OC (2004): Non-invasive pressure support ventilation in patients with respiratory failure due to severe acute cardiogenic pulmonary edeme. Respiration. 71:144-51.
66. Van Diest I, Thayer JF, Vandeputte B et al. (2006): Anxiety and respiratory variability. Physiol Behav. 89:189-195.
67. Wahba RW, Tessler MJ, Béique F et al. (1996): Changes in PCO_2 with acute changes in cardiac index. Can J Anaesth. 43:243-5.
68. Walters K, Rait G, Petersen I, et al. (2008): Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using general practice research database. Eur Heart J. 29:2981-8.
69. Williamson CA, Sheehan KM, Tipirneni R et al. (2015): The association between spontaneous hyperventilation, delayed cerebral ischemia, and poor neurological outcome in patients with subarachnoid hemorrhage. Neurocrit Care 23:330-8.
70. Yamashiro Y and Kryger MH (1993): Review: sleep in heart failure. Sleep. 16:513-23.
71. Yasue H, Nakagawa H, Itoh T et al. (2008): Coronary artery spasm—clinical features, diagnosis, pathogenesis, and treatment. J Cardiol. 51:2-17.
72. Zhang H, Shan C, Zhang YU et al. (2015): Blood gas analysis of the coronary sinus in patients with heart failure. Biomed Rep. 3:379-82.
73. Zile MR, Baicu CF and Gaasch WH (2004): Diastolic heart failure – Abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med. 350:1953-9.

A hipokapnia és a pszichés stressz ördögi köröket eredményezhet súlyos betegekben az energiaegyensúly megbomlása következtében

A hypocapnia kórélettani jelentősége erősen alulbecsült mind a funkcionális, mind az organikus megbetegedésekben. A széndioxidszint változásai azonnal megjelennek a citoplazmában is, ami hirtelen pH változásokat okoz. A kompenzáló mechanizmusok viszonylag lassúak, így az intracelluláris alkalózis vagy acidózis órákon/napokon keresztül befolyásolhatja a szövetek anyagcseréjét. A hiperventilációs alkalózis növeli az anyagcsere energia/O_2 igényét, ugyanakkor az ATP termelés hipofoszfatémia miatt gyakran csökken. Egy fiatal, egészséges szervezet kényelmesen kiszolgálja a megnövekedett energiaigényt. Az aktív és passzív membrán Ca^{2+} motilitás miatt a kortikospinális és neuromuszkuláris rendszer excitábilitása nő és funkcionális betegségek alakulhatnak ki, de a szövetek szerkezetileg változatlanok maradnak. Ezzel szemben például a kritikusan beteg szívizom nem képes kielégíteni az akut hypocapnia okozta megnövekedett energiaigényt. Ördögi körök alakulhatnak ki előre és hátrafelé ható hibával; az energiahiánnyal párhuzamosan nő a pulmonális éknyomás, ami tüdőödémához vezethet. Kritikusan súlyos betegség esetén a hipokapnia fatális kimenetelű ördögi köröket generálhat számos más betegségben is. A szimpatikotónia és hipokapnia növeli az arousalt és energetikailag instabillá teszi a biológiai rendszereket, így az ördögi körök kialakulása csaknem törvényszerű. A szomatikus és pszichés folyamatok kölcsönösen befolyásolják egymást, így pszichoszomatikus vagy szomatopszichés betegségek jöhetnek létre. Az energiaellátás biztosításának képessége fontos választó vonal lehet az organikus és funkcionális betegségek között.

Kulcsszavak: kardiogén tüdőödéma, energiaigény, hipokapnia, pszichoszomatikus pathomechanizmus, circulus vitiosus