Dear friends of clinical journal club - load the file down at https://www.mdc-berlin.de/cjc. This website also gives you access to my seminar on Wednesdays 16:00 English and 17:00 German. You need to click on *Besprechung beizutreten*. If it fails to work immediately, keep on clicking.

A 79-year-old man with heart failure with reduced ejection fraction and atrial fibrillation presented to the emergency department with a 2-week history of shortness of breath. On physical examination, there was an irregular heart rhythm, crackles in both lungs, and pitting edema in both legs up to the mid-thigh. The jugular venous pressure was estimated to be 17 cm of water (normal value, < 4 cm of water). When firm, sustained pressure was applied to the center of the abdomen, there was a sustained increase in the jugular venous pressure of more than 3 cm of water for more than 10 seconds while pressure was applied. What is the mechanism of this physical exam finding? You are offered: Decreased compliance of the pericardium, Impaired filling or contraction of the right ventricle, Left-to-right shunting, Severe tricuspid regurgitation, and Ventricular interdependence. Try the maneuver out! Amylin is another gastrointestinal hormone from the pancreas associated with diabetes. Amylin delays gastric emptying, decreases food intake, lowers glucagon secretion, causes vasodilatation, and decreases osteoclastic activity. An amylin agonist, called cagrilintide, has been developed. Semaglutide at a dose of 2.4 mg has established weight-loss and cardiovascular benefits, and cagrilintide at a dose of 2.4 mg has shown promising results in early-phase trials; the efficacy of the combination (known as CagriSema) on weight loss in persons with either overweight and coexisting conditions or obesity is unknown. In a phase 3a, 68-week, multicenter, double-blind, placebo-controlled and active-controlled trial, investigators enrolled adults without diabetes who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher or a BMI of 27 or higher with at least one obesity-related complication. Participants were randomly assigned in a ratio of 21:3:3:7 to receive the combination of semaglutide at a dose of 2.4 mg and cagrilintide at a dose of 2.4 mg, semaglutide alone at a dose of 2.4 mg, cagrilintide alone at a dose of 2.4 mg, or placebo, plus lifestyle interventions for all groups weekly. The coprimary end points were the relative change in body weight. The combination, cagrilintide plus semaglutide beat all other groups. Next, the same single-shot combination was tested in obese, type-2 diabetic

patients. The combination caused substantial weight loss, hemoglobin A1C dropped by 2 percent, and blood sugars were greatly improved. Normal saline contains 154 mmol/L Na and 154 mmol Cl per liter, while Ringer's lactate contains less about 30 mmol/L less Cl and lactate instead. Saline causes "some" hyperchloremic acidosis and Ringer's less so. Whether lactated Ringer's solution is clinically superior to normal saline for routine intravenous administration of fluids is uncertain. In an open-label, two-period, two-sequence, cross-sectional, cluster-randomized, crossover trial, investigators assigned hospitals in Ontario, Canada, to use either lactated Ringer's solution or normal saline hospital-wide for a period of 12 weeks. After a washout period, hospitals switched to the other fluid for 12 weeks. The primary outcome was a composite of death or readmission to the hospital within 90 days after the index admission. Hospital use of lactated Ringer's had no effects on any outcomes, compared to use of saline solution. Spinomuscular atrophy (SMA) is a feared Mendelian X-linked muscle disease causing death in infancy. SMA is caused by recessive loss-of-function variants in the gene *SMN1* and reduced expression of the ubiquitously expressed protective SMN protein. A paralogous gene, *SMN2*, is retained in a variable number of copies but cannot fully compensate for loss of *SMN1* because it contains a nucleotide variant that causes alternative pre-mRNA splicing, which results in the excision of exon 7 and a truncated, rapidly degraded protein. Risdiplam is an orally administered small molecule RNA-splicing modifier that could fix the defective exon 7 in *SMN2* and restore the SMN protein in boys with SMA. Investigators conducted an open-label study of daily oral risdiplam (with the dose adjusted to 0.2 mg per kilogram of body weight) in infants 1 day (birth) to 42 days of age with genetically diagnosed SMA but without strongly suggestive clinical signs or symptoms. The primary outcome, assessed in infants with two SMN2 copies and a baseline ulnar compound muscle action potential (CMAP) amplitude of at least 1.5 mV, was the ability to sit without support at month 12. The risdiplam treatment seemed promising. The apparent effects of risdiplam were evident across the spectrum of patients treated, but infants with higher *SMN2* copy numbers and compound muscle action potential (CMAP) amplitudes appeared to have more favorable responses. The N Engl J Med review is on metabolic dysfunction–associated fatty liver disease (MAFLD). MASLD has become the most common chronic liver disease, affecting up to 38% of the adult

population worldwide. The N Engl J Med patient is a 28-year-old woman with a progressive lung disease causing severe hypoxemia and pulmonary hypertension in the face of a normal capillary wedge pressure. A classic triad of CT findings was identified: centrilobular ground-glass nodules, interlobular septal thickening, and mediastinal lymphadenopathy. In the Lancet, we again confront mineralocorticoid-receptor (MR) blockade. MR activation not only involves aldosterone-induced sodium reabsorption, potassium elimination, and volume expansion with hypertension, but also has been implicated in many adverse cardiovascular effects. Thus, two large trials of spironolactone were conducted in hemodialysis patients to test whether-or-not cardiovascular deaths could be reduced. Both trials were negative; spironolactone over years did not reduce cardiovascular mortality in dialysis patients. FGF21 is a hepatic hormone with numerous salubrious effects that could reduce MASLD. Efruxifermin is an FGF21 agonist. Safety and efficacy of once weekly efruxifermin were tested in a Lancet study and MASLD was successfully reduced. Next, a Lancet Commission informs us how liver cancer could be reduced world-wide. Hepatitis vaccination, treating hepatitis C, drinking less alcohol, and combating MASLD were high on the list of things to do. Liquid biopsies to find cancer are all the rage in the popular press but the efficacy is less than outstanding. In Science Magazine, we find out that analyzing platelets for circulating tumor DNA and RNA could be a better approach. In Washington Post, we are informed that it is rude to ask someone if they are squirting *Ozempic* or other GLP-1 agonists.

Join me on Wednesday, August 20 for another stunning, orally presented, clinical journal club, 16:00 in English and 17:00 in German.

Sincerely, Fred Luft

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