Good morning, ladies and gentlemen. Mr. Chairman, it is my great pleasure, but mainly it is an honor for me to be invited for lecturing this audience. I hope I can inform you about some new aspects concerning myocardial protection. The title of my lecture is “Custodiol Cardioplegia: A Single-Dose Hyperpolarizing Solution.” The impact of a low-sodium solution on electrophysiology, physiology, solution's composition and experimental results, mode of administration, clinical results, and last but not least, the take-home message is demonstrated step by step.

The first aspect is related to electrophysiology, which is included in the title—hyperpolarization. What does it mean? We have calculated the membrane potential, especially for this congress (Figure 1). How does the membrane potential change, if you administer Histidine-Tryptophan-Ketoglutarate solution? I always call it HTK solution, since Custodiol® is the item being given by the manufacturer. Since HTK solution can be used at cold as well as tepid temperatures, the membrane potential changes. We have a membrane potential of around $-50\,\text{mV}$ at $8^\circ\text{C}$. And if you administer the solution at $35^\circ\text{C}$, the membrane potential increases. For calculation of the membrane potential, we used the following data: intracellular sodium concentration of 15 mMol, 120 mMol potassium, and 135 mMol chloride. So that is the solution's influence on the electrophysiology. But, to be honest, it plays no role in clinical use. This is only of scientific interest.

Let’s move to physiology. Firstly, low-sodium solutions, how do they work? Primarily, it is an action potential of a muscular fiber, and it starts with a fast depolarization (Figure 2). If you significantly reduce sodium, the fast inward current is inhibited and the heart is arrested. Secondly, in our Department of Physiology in Göttingen in the late 1960s, Dr. Bonhoeffer could demonstrate that if you perfuse a heart at $35^\circ\text{C}$ with different solutions, low-sodium solution effects the lowest energy turnover (1). The solution's influence on the electrophysiology. But, to be honest, it plays no role in clinical use. This is only of scientific interest.

Thirdly, there is a problem with any low-sodium solution. Most of you well remember the calcium paradox phenomenon being induced by calcium-free solutions. Therefore, I must explain why this low-sodium solution will never lead to a calcium paradox, because of a natural law, which seems to be a little bit difficult, but I will try to explain the equation very slowly (Figure 3).

You see this special law of nature. The sodium intracellular square divided by sodium extracellular square is the same if you divide the intracellular calcium concentration by extracellular calcium concentration. What parameters do we know? We know calcium extracellular and sodium extracellular. And I have chosen a calcium concentration at 1.5 mMol to solve this equation and the sodium concentration at 150 mMol, to make it very simple. What happens now with the appropriate calcium concentration if we reduce the sodium content to 1/10? We know the sodium concentration and the result of this equation, and we have only to look for the calcium concentration. And the calcium concentration is 0.015 mMol. That means, if you reduce the sodium content to 1/10, you have to reduce the calcium concentration to 1/100.

If you use the low-sodium solution, the sodium chloride leads to an osmolarity of 30 mOsmol/L in comparison to a high-sodium solution at 115 mMol (Figure 4). In this case the NaCl osmolarity is 230 mOsmol/L. However, the upper limit of osmolarity in a cardioplegic solution should be within the physiological range, being 300 mOsm/L. So now you can realize that with low-sodium solution an osmotic space is available to add numerous highly concentrated substances, which cannot be added to a high-sodium solution, since the osmotic space is restricted. And among these substances, there is a buffer. That means only low-sodium solutions offer the potential to add a highly concentrated buffer.
Now, ladies and gentlemen, let’s move to the problem to use a buffer (Figure 5). The efficiency of a buffer depends at first on the buffer concentration. And most probably you may smile, if I argue, even water acts as a buffer. Imagine you have 10,000 L of water, pure water, and you add one drop of an acid inside, the pH remains constant. But, if you have only 1 mL of water and put the same drop of acid inside, the pH will immediately change. That means buffer concentration plays a role. Therefore, if people have used only 10 mMol/L bicarbonate, e.g., in St. Thomas’ solution, it is almost nothing. Some people recommend Tris(hydroxymethyl)-ammiomethan (THAM) as buffer. THAM leads to a further problem concerning the efficiency of a buffer and the relation of its pK value to the appropriate pH range, in which the buffer shall act.

Now we have to ask what suitable buffers may be used? We have hemoglobin, THAM, bicarbonate—but bicarbonate does only act under aerobic conditions—histidine, and

![Figure 1. Temperature dependent changes of the membrane potential of the HTK protected myocardium.](image1)

![Figure 2. Drafted influence of electrolytes on the membrane action potential of the myocardial muscle fiber (left) and influence of different arresting solutions on myocardial oxygen consumption at normothermia. (Bret: unbuffered Bretschneider solution).](image2)

![Figure 3. Relation between Na and Ca concentration in a low-Na cardioplegic solution.](image3)

![Figure 4. Significance of high or low Na concentrations on the osmotic space for effective buffering.](image4)

![Figure 5. Suitable buffer substances for cardioplegia and their pK values.](image5)
carnosine. You will agree that carnosine seems to have the optimal pK value of 6.8, because the pH of ischemic myocardium changes from about 7.4, depending on the ischemic time or the ischemic stress, respectively, to 6.0 or even less. So the buffers should act between 7.0 and 6.0. Therefore, carnosine seems to be superior to histidine.

We were very optimistic to use carnosine, a wonderful buffer. Carnosine is a double molecule, consisting of histidine and alanine. Since the pK value of 6.8 was almost perfect, we performed some experiments related to energetics, especially we looked for the adenosine triphosphate (ATP) degradation during ischemia. We could demonstrate that carnosine was superior to histidine. Therefore, we were almost forced to make experiments to resuscitate the myocardium after 5 hours of ischemic arrest, with short-term reperfusion. And that was the result (Figure 6).

You see morphology protected by histidine and its edema and the endothelial swelling. On the other hand, carnosine completely failed. All muscular fibers were disrupted and an enormous loss of myoglobin occurred, while the heart was getting pale, and an enormous loss of creatine kinase (CK) and CK-MB happened. So carnosine failed. We have never investigated why it failed, but we could only demonstrate that it failed.

So, therefore, we used histidine, and this, you see, is the composition of the solution (Figure 7): low sodium, traces of calcium as being presented before, slightly increased potassium and magnesium, some tryptophan, ketoglutarate, and mannitol. But, the important component is the buffer, the histidine buffer. Biochemically, histidine also exists in the hemoglobin chain, in which are 9 histidine molecules among a total of 146 amino acids.

Besides the buffer effect, histidine acts as free radical scavenger, so that the solution has two scavengers: the first one is histidine and the second one is mannitol. Therefore, using this solution, there’s no danger for an ischemic-reperfusion injury, since the concentrations of scavengers are too high.

Now let’s move to a further and important aspect, the mode of administration (Figure 8). We always speak about cardioplegic solutions and forget the modes of administration, and I will demonstrate some special aspects. For administration, we have used roller pump and gravity in patients. And you see, during cardioplegic perfusion, the difference between the arterial pO2 and the coronary venous pO2 decreases. Now you may say, “Well, it depends on the temperature.” No, I’m sorry, since temperature will equilibrate within 2 or 3 minutes. Such decrease of pO2 differences has a clinical aspect and is more or less of scientific importance.

We used HTK solution in patients with aortic valve diseases and myectomies. After 7 minutes, we have reached...
an oxygen consumption of 1 mL/min for the total heart. And if we premise a heart weight of about 400 g, it means .25 mL/min/100 g. And that is exactly the value we have measured in animal experiments. Now people argue that this phenomenon is a HTK related problem. However, that is incorrect. We have therefore used St. Thomas’ solution and at that time, Dr. Braimbridge recommended only a 3-minute-perfusion. After 3 minutes, we got the same results as with HTK.

Why, ladies and gentlemen, is it necessary to reduce the O₂ consumption as much as possible? Because of the following biological fact: the lower the O₂ consumption is, the lower is the myocardial creatine phosphate content.

Figure 9. Correlation between myocardial oxygen consumption and myocardial creatine phosphate content.

Figure 11. Impact of reperfusion on CK and lactate levels.

Concerning this aforementioned aspect, there was a wonderful study in the mid-1990s. They used video intensity signals for evaluation of antegrade perfusion and no difference between left and right ventricle occurred. But, what is with retrograde perfusion? They could demonstrate an inferior protection of the right ventricle using video intensity signals. These data prove our speculations (3).

And now let us focus on replegia in neonatal hearts. It’s a study from South Korea (4). They used a mitochondrial scoring. They compared Del Nido solution, being administered every 40 minutes, with HTK solution, also administered every 40 minutes, and HTK without replegia. If there is no replegia, the morphological injury is less pronounced in comparison to others. So it seems—and there are numerous other studies—that the neonatal heart is more sensitive to replegia than the adult heart.

In Beijing, a comparative study in neonates between St. Thomas’ and HTK solution, both crystalloid solutions, was performed (5). In the St. Thomas’ group, cardioplegic reperfusion was done every 30 minutes, but no replegia in the HTK group. Cross-clamp time was 170 minutes in the HTK group vs. more than 3 hours in the other group. You realize the time-saving effect and that the outcome regarding mortality and CK loss, on the second day, were significantly lower.

Dr. Angeli from Bologna did a study in arterial switch operations (6). She administered HTK solution, 50 mL within 7 minutes and did not replegia. Cross-clamp time lasted almost 100 minutes, and the troponin I loss was highest after 6 hours and then it decreased. A study from Russia demonstrated no replegia in newborns aged only 7 hours (7). After about 12 hours, the systemic lactate level has already normalized.

Now let’s go back to only one slide concerning experimental results. We have arrested dog hearts at different ischemic stress using different solutions (Figure 10). It is obvious that using HTK solution, the ATP contents after declamping of the aorta were always higher in comparison to others. Why is this result important? Is it only a scientific problem or has it a practical consequence? To my opinion, it has a clinical impact (Figure 11).
Focusing on low-output syndrome, we must establish that if an intraoperative low-output syndrome happens, creatine phosphate and ATP contents have critically decreased, whereas the myocardial edema has increased during ischemia. That is the first option. The second one is a stunned myocardium which seldom happens. From the clinical aspect, you cannot intraoperatively evaluate whether it is a failure due to low energy or it’s a stunned myocardium.

But, we should not forget that there are also postoperative reasons why a low output syndrome occurs postoperatively after hours at the intensive care unit. After declamping of the aorta, creatine phosphate will increase within minutes, while the ATP content remains constant for hours. However, an intracellular edema develops within hours, and this intracellular edema will impair the coronary flow, which may lead to a secondary ATP decrease and which might now get crucial for the myocardium. This flow chart may explain why a low output syndrome first happens after hours.

Now some clinical results from adults. I have already shown clinical results from neonatal hearts. Now, these results in mitral valve surgery were published in 2012. Two thousand seven hundred patients were operated in a German center, and a low output syndrome occurred in only 1.4% of the patients. In-hospital mortality rate was 1.2, and the 5-year survival was more than 80%. You see, intraoperative balloon pumping plus ECMO was necessary in only four cases of these 2,700 patients.

A study, being published at the Florida Valve Meeting 2014, demonstrated a comparative study between single-dose HTK and blood cardioplegia. And again, they could demonstrate the time saving effect, since there’s no need for cardioplegic reperfusion. All other results were equivalent. But, they mentioned that they had significantly less postoperative problems in the HTK group concerning gastrointestinal complications, new pacemaker implantations, and dialysis. A study from Bari in Italy compared HTK and blood cardioplegia in acute aortic dissections (8). HTK was not re-administered in 150 minutes, while in the blood cardioplegic group reinfusion was done every 20–30 minutes. Analyzing troponin I loss, it was higher in the blood cardioplegic group.

Let’s comment on troponin I loss looking at two studies. One prospective randomized study from Norway (9), and the other one from the aforementioned study from Bari. Both studies could demonstrate a significant correlation in the HTK group concerning cross-clamp time and troponin I or T loss, while—and that is very interesting—in the blood cardioplegic group, no correlation could be analyzed. These results are, among others, a reason why the Food and Drug Administration (FDA) does not accept the troponin loss as parameter for evaluation of the quality of a cardioplegic method.

So, one question is often asked: low-sodium solution and systemic hyponatremia? It sometimes happens, but I can give you brand new data from our unit. We have done prospective and retrospective analyses on the systemic sodium content after systemic HTK administration. The retrospective study showed equivalent data in comparison to the prospective study. But, in the prospective study, we additionally looked for the osmolarity, which is the most important parameter in combination with systemic hyponatremia. In this prospective group no patient showed systemic hypoosmolarity.

Finally some data regarding heart transplantation (10). The mean ischemic time of these almost 1,300 transplants was 194 minutes, and the primary graft failure was only 7%. The failure rate is influenced by the cross-clamp time. You see, after more than 5 hours, there is a significant increase in primary graft failure rate.
Now, ladies and gentlemen, I finally come to the take home message. Due to major advantages in anesthesiology, intensive care medicine, and surgery, today patient’s safety and surgeon’s convenience have evolved into primary evaluative criteria for cardioplegia. That is the update of the situation. Any cardioplegic method impacts both of these parameters.

Scientifically, the need of cardioplegic reperfusions reflects, to my opinion, inadequate potency of any applied method, thereby reaching the limit of myocardial resuscibility early. In all cases with prolonged cross-clamp time, cardioplegia without replegia means time saving and, as I mentioned before, a paradigm shift. Today ambitious modern cardiac surgery is feasible without cardioplegic reperfusion. I thank you very much for your attention.

REFERENCES


