CUSTODIOL®

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CUSTODIOL®

HTK - Bretschneider®

Your clear **Solution**

for Organ Protection

CUSTODIOL®
The only solution for all organs

In situ protection

- Heart surgery
- Kidney tumour resection
- Preservation of blood vessels

Organ transplantation

- Multi-organ procurement
- Protection of all kinds of organs (including those from ECD and DCD)
- Split liver donation

CUSTODIOL®
Worldwide accepted as a standard in organ protection

- Original **Histidine-Tryptophan-Ketoglutarate solution (HTK)** developed by Professor Hans J. Bretschneider and Dr. Franz J. Köhler
- **"Ready-to-use"**: no filters or additives are necessary
- All components are naturally occurring physiological substances (except for the inert mannitol)
- Preferred protection solution in **over 90 countries** worldwide
- **Over 3 Million** performed surgeries
- Standard perfusion and preservation solution of EUROTRANSPLANT
- **Clinically proven:** Over 900 peer-reviewed articles prove safety and reliability

CUSTODIOL®

The Clear Solution designed for safety and comfort

- **Low concentration of potassium:**
  no need for a pre-flush
- **Low concentration of sodium and calcium:**
  no unwanted intracellular activities initiated by the entry of Na+ or Ca2+
- **High histidine buffer:**
  strong buffer capacity prevents metabolic acidosis
- **Tryptophan:** protection of cell membranes
- **Ketoglutarate:** energy substrate for production of ATP
- **Mannitol:**
  osmotic diuretic protecting against oedema formation
- **Low viscosity:**
  fast cooling and efficient perfusion of organs
- **Physiological osmolarity:**
  no formation of oedema, no neurological implications
- **Radical scavengers:**
  Histidine and mannitol act as anti-oxidants
- **Intracellular solution:**
  The electrolyte composition is close to cytoplasmic levels
- **High systemic tolerance:**
  All constituents are naturally occurring physiological substances (except for the inert mannitol)
- **High ischemic tolerance:**
  Even at increasing temperatures at end of surgery
- **Crystalloid solution:**
  allows a blood-free view field for the surgeon
- **Ready to use:** No additives, no filtering needed

The only solution for Cardioplegia and Transplantation

Right packaging for each indication

- 1 litre bag
- 2 litres bag
- 5 litres bag

CUSTODIOL®

Manufactured in Germany by:

- Family-owned and managed company with long history and experience
- High sophisticated state-of-the-art GMP-production (capacity of more than 6.000 litres/day)
- Own certified API production
- Own Research and Development Center
- High specialization in the field of hospital and ICU medicine
- Numerous interdisciplinary joint projects with internationally accepted universities and hospitals
- Worldwide Partner and Distribution network

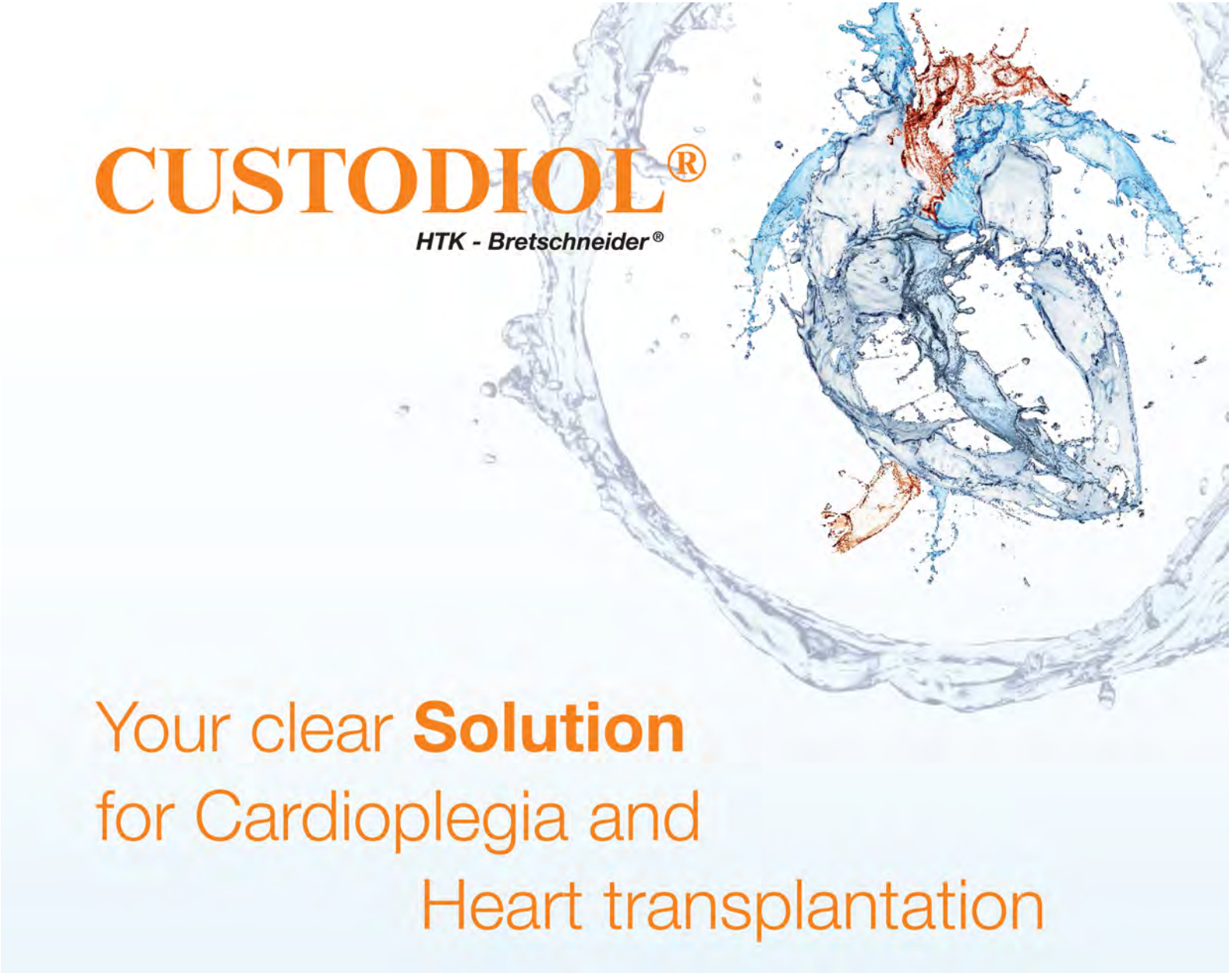
CUSTODIOL®

The Clear Solution designed for safety and comfort

Composition: 1,000 ml of the solution contain: 0,8766 g sodium chloride (15.0 mmol), 0.6710 g potassium chloride (9.0 mmol), 0.8132 g magnesium chloride x 6 H_2O (4.0 mmol), 27.9289 g histidine (180.0 mmol), 3.7733 g histidine hydrochloride monohydrate (18.0 mmol), 0.4085 g tryptophane (2.0 mmol), 5.4651 g mannitol (30.0 mmol), 0.0022 g calcium chloride x 2 H_2O (0.015 mmol), 0.1842 g potassium hydrogen 2-ketoglutarate (1.0 mmol). Potassium hydroxide solution. Water for injection
Indication: Cardioplegia in connection with cardiosurgical operations, organ protection during operations under ischemia (heart, kidney, liver), preservation of organ transplants (heart, kidney, liver, lung, pancreas), together with venous or arterial segments. Multi-organ protection.
Contraindications: None known. **Side Effects:** None known.
Dosage guidance, mode and duration of use: Please see detailed instructions for use and specialist information. Warning: **CUSTODIOL®** is not intended for intravenous or intra-arterial administration, but only for selective perfusion of the relevant organs and for surface cooling and preservation of the donor organ en route from donor to recipient. **CUSTODIOL®** must therefore not be used for systemic infusion!
Presentation and pack sizes: Bags of 1,000 ml, 2,000 ml and 5,000 ml. Prescription Drug. As at 08/2015

CUSTODIOL®

HTK - Bretschneider®



Your clear **Solution**
for Cardioplegia and
Heart transplantation

CUSTODIOL®

Cardioplegia with unique benefits

- **Cardioplegia:** Professor Bretschneider broadened the definition of “cardioplegia” to be a synonym for “myocardial protection”. The histidine-tryptophan-ketoglutarate solution (HTK) **CUSTODIOL®**, has been originally designed in order to provide an optimal myocardial protection
- **One of the only two well-documented methods of cardioplegia:** Bretschneider’s and Buckberg’s principles of cardioplegia are the only techniques, which offer a proven track record of published clinical studies
- **Nondepolarizing cardiac arrest:** The low-to-moderate content of electrolytes (“intracellular”-type cardioplegic solution, 15 mM sodium) mean less cellular stress during cold ischemia, especially since the cell membranes are protected by tryptophan
- **A single/initial application** applied over the period of 6-8 minutes **is sufficient for up to 180 minutes of myocardial ischemia**
- **Superior energetic protection (ATP):** Energy substrates and high buffering capacity offer the basis for both anaerobic energy supply during ischemia and full return to function upon reperfusion

Comparison of cardioplegic concepts

	CUSTODIOL®	Blood-based
Composition	K^+ low, Na^+ low	K^+ high, Na^+ low
Incidence of ventricular Arrhythmia[1]	33%	72%
Spontaneous Defibrillation[1,2,4]	90%	26%
Oedema formation[3]	27%	54%
Mortality rate[4]	1.3%	NN
Cross clamp period without repeat cardioplegia[4,5]	120-180 minutes	Repeated doses of cardioplegia (<20min)
Transplantation	yes	no

1) Hachida M, Nonoyama M, Bonkohara Y, Hanayama N, Saitou S, Maeda T, Ohkado A, Lu H, Koyanagi H. Clinical assessment of prolonged myocardial preservation for patients with a severely dilated heart. Ann Thorac Surg. 1997 Jul;64(1):59-63.

2) Sakata J, Morishita K, Ito T, Koshino T, Kazui T, Abe T. Comparison of clinical outcome between histidine-triptophan-ketoglutalate solution and cold blood cardioplegic solution in mitral valve replacement. J Card Surg. 1998 Jan;13(1):43-7.

3) Kim S, Lee YS, Woo JS, Sung SH, Choi PJ, Cho GJ, Bang JH, Roh MR, Histidine-tryptophan-ketoglutarate Versus Blood Cardioplegic Solutions: A Prospective, Myocardial Ultrastructural Study. Korean J Thorac Cardiovasc Surg 2007;40:8-16

4) Misfeld M, Davierwala P. Crystalloid-based cardioplegia for minimally invasive cardiac surgery. Semin Thorac Cardiovasc Surg. 2012 Winter;24(4):305-7.

5) Matzelle SJ, Murphy MJ, Weightman WM, Gibbs NM, Edelman JJ, Passage J. Minimally invasive mitral valve surgery using single dose antegrade Custodiol cardioplegia. Heart Lung Circ. 2014 Sep;23(9):863-8.

CUSTODIOL®
Cardioplegia for all situations

- **Protection even in the case of coronary heart disease (CHD):** excellent equilibration of the extracellular space provides a full protection of the whole heart
- **Recommended solution for highly complex procedures:** the preferred solution for minimally invasive surgery (MICS), neonates (ASO), redo-, and combined operations
- **Excellent preservation of bypass grafts:** during coronary artery bypass grafting (CABG) **CUSTODIOL®** can be used for the storage of blood vessels
- **Safety for the young heart:** less risk of damage to the tunica intima of neonatal hearts, because no intermittent reperfusions are required for over 2 hours
- **Excellent recovery of the young heart:** gentle and fast post-ischemic recovery of the neonatal myocardium

CUSTODIOL®
Heart transplantation (HTx)

- **The proper mixture to combat cold ischemia/ reperfusion injuries:** originally designed for cardioplegia. Same physiological principles apply to the long-term preservation of the graft (cardioplegia = myocardial protection)
- **Standard in HTx:** only three preservation solutions are clinically accepted (HTK, UW, Celsior)
- **Used in tens of thousands of cases:** a single German HTx centre transplanted over 1200 organs successfully (within 15 years)

Myocardial protection during MICS

A single dose of antegrade CUSTODIOL® crystalloid cardioplegia is a safe and effective strategy to protect the myocardium during Minimal Invasive Valve Surgery[6]

Operative data	Evaluation
In-hospital mortality	0 %
ICU stay	Short
Myocardial cytonecrosis enzymes (CK-MB, Lactate)	No significant increase was found
Inotropic support >24 h	Mild-to-moderate postoperative support
Neurologic complications	Only one patient (not related to HTK)
Occurrence of renal complications	Very low
Incidence of AF (postoperative atrial fibrillation)	Low
Overall clinical outcomes	Excellent

After aortic occlusion, one single dose of CUSTODIOL® solution is delivered for a period of 6 to 8 minutes (20-25 mL/kg) into the aortic root with a perfusion pressure (aortic root pressure) of 40 to 60 mm Hg. No additional cardioplegic doses are required

Hemodilution after a large volume of cardioplegia infusion is an important point. To maintain a stable hemoconcentration during the perioperative period, a careful ultrafiltration during extracorporeal circulation as well as a strict use of diuretic drugs in intensive care and ward units was used. This approach enabled the authors to use a minimal amount of blood transfusion during the postoperative course

6) Savini C, Murana G, Di Eusanio M, Suarez SM, Jafrancesco G, Castrovinci S, Castelli A, Di Bartolomeo R. *Safety of single-dose histidine-tryptophan-ketoglutarate cardioplegia during minimally invasive mitral valve surgery.* Innovations (Phila). 2014 Nov-Dec;9(6):416-20.

Myocardial protection of the young heart

The usage of CUSTODIOL® helps minimizing the frequency of interruptions of the surgical procedure[7]

	CUSTODIOL®	Blood group
Number of doses given	1	5
Cardiopulmonary bypass time (min)	160	188
Aortic cross-clamp time (min)	93	112
Mortality at 30 d (%)	0	2.3
Total hospital stay	23	25

Blood and metabolic outcomes were equal. Typically, in the **CUSTODIOL®** group, TnI level had a peak in the early hours after CPB with a rapid decrease within the first 24 hours **CUSTODIOL®** was infused anterograde according to the following protocol: temperature 5 to 8°C; 1 ml of solution per minute and per gram estimated heart weight (infant ≈ 0.6% of bodyweight); and perfusion pressure initially 80 to 90 mm Hg, after cardiac arrest 30 to 40 mm Hg for 6 minutes. The right atrium was opened and the cardioplegia was completely aspirated outside the bypass circuit to avoid hemodilution

7) Giordano R, Arcieri L, Cantinotti M, Pak V, Poli V, Maizza A, Melo M, Assanta N, Moschetti R, Murzi B. *Custodiol Solution and Cold Blood Cardioplegia in Arterial Switch Operation: Retrospective Analysis in a Single Center.* Thorac Cardiovasc Surg. 2016 Jan;64(1):53-8.

Myocardial protection during transplantation

Efficacy confirmed in more than 1290 Heart Transplant Recipients[8]

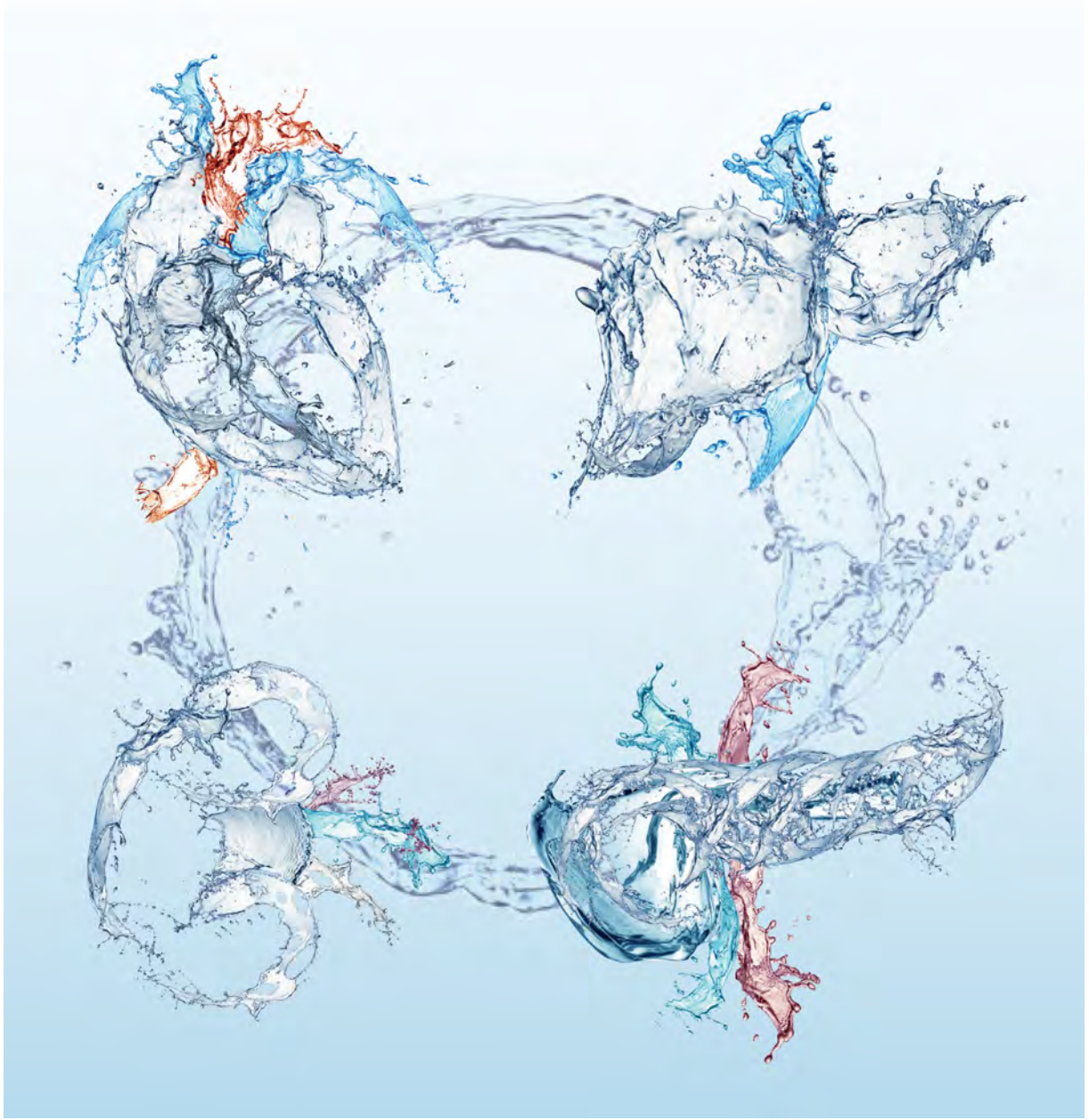
Cold Ischemia Time (CIT)	
Median	194.4 min
Standard deviation	±40.4 min

30-day mortality	
Overall	9%
CIT > 240 min	13%

Data recorded between 1989 and early 2004 at a single transplant centre (Bad Oeynhausen, Germany) where the greatest number of heart transplants in the world were performed during that time. These data represent the entire experience of the centre, with no cases excluded.

Donor heart procurement was performed as follows: At the time of explantation, 50 ml/kg body weight of **CUSTODIOL®** was used for flushing and the heart was stored in 1000 ml of **CUSTODIOL®**. Following cross-clamping of the ascending aorta, the perfusion pressure of **CUSTODIOL®** was maintained at 60 mmHg initially, and maintained at 40 mmHg for a period of 7 minutes after cardiac arrest. This follows a perfusion rate of 1 ml/min per gram of heart weight, up to a total amount of 3000 to 4000 ml used for adults

8) Tjang YS, van der Heijden GJ, Tenderich G, Grobbee DE, Körfer R. *Survival analysis in heart transplantation: results from an analysis of 1290 cases in a single center.* Eur J Cardiothorac Surg. 2008 May;33(5):856-61



Comparing Custodiol with St Thomas

	KHB	HTK	STH	NIH
Na	143	15	129	98.9
Cl	128	50	140	107.8
K	5.94	10	16	30
Mg	1.19	4	16	0
Ca	2.57	0	1.2	1
Histidine	0	198	0	0
HCO_3	25	0	37	22
PO_4	1.19	0	0	0
SO_4	1.19	0	1.2	0
Tryptophan	0	2	0	0
Glutarate	0	1	0	0
Glucose	5.56	0	0	152.6
Mannitol	0	30	0	68.6
Procaine	0	0	1	0
Lidocaine, mg/l	0	0	0	20
Nitroglycerin, mg/l	0	0	0	0.5
Osmolarity, mosm/kg H_2O	314	309	341	452

Unless otherwise indicated values are given as mmol/l.

Kober et al., Eur Surg Res 1998;30:243–251

Parameter	Custodiol	St Thomas
Type of solution	intracellular solution (low sodium)	extracellular solution (high sodium)
How does it work	HTK is an hyperpolarizing solution (low sodium, moderate potassium concentrations), diastolic heart arrest	STH is depolarizing the myocardial membranes (high sodium, high potassium), diasystolic heart arrest
Practical issues	HTK is ready to use	STH has to be prepared before the operation: HCO3 must be added in order to adjust the pH
Additives	none	Procaine: Animal models showed that during cardiac arrest the permeation of H-ions from intra to extracellular space was impaired. Hence a strong buffer is needed, which protects the extracellular space
Mode of administration	Single dose, cold ischemia times for up to three hours	Repetitive administration, has to be given every 20-45 minutes (surgical procedures must be suspended during each 2 minute infusion)

ASAIO Journal 2008

The Myocardial Protection of HTK Cardioplegic Solution on the Long-Term Ischemic Period In Pediatric Heart Surgery

JINPING LIU, ZHENGYI FENG, JU ZHAO, BO LI, AND CUN LONG

HTK and STH in pediatric surgery

- Study period: 2004-2007
- Groups: H(Custodiol) n=63, S(St Thomas) n=55
- Type of operations:
- Biventricular outflow tract reconstruction (Nikaidoh, REV), double-switch surgery for corrected transposition of the great arteries (cTCA), arterial switch Operation (ASO) → Long term myocardial ischemia
- Administration: Custodiol was cooled at 4°C-8°C and perfused via the aortic root at an initial perfusion pressure of 80-100 mm Hg. When the myocardium was at a standstill, the perfusion pressure was maintained to 40-60 mm Hg, and the HTK soiution was infused over 5-7 minutes. All cases were perfused with the Single dose at 40-50 ml/kg during aortic cross-clamping. During perfusion of HTK solution, hemodilution and electrolyte imbalance were avoided by aspirating all the crystalloid soiution into the C.A.T.S directly from the coronary sinus.

Table 1. Composition of Different Cardioplegic Solutions

Substrate (mM)	(S) St. Thomas*	(H) HTK†
Na^+	116	15
K^+	16	10
Ca^{2+}	1.2	0.02
Mg^{2+}	16	4
Sodium bicarbonate	10	0
Histidine	0	180
Tryptophan	0	2
Ketoglutarate	0	1
Mannitol	0	30
Theoric osmolality (mOsm/L)	318	310

* Extracellular solution.
† Intracellular solution.

Table 2. Surgical Procedures in the Two Groups

Procedures	Group H (n = 63)	Group S (n = 55)
Nikaidoh/REV	8/1	2/1
Double switch	2	5
ASO	18	12
IAA	6	2
TAPVC	7	12
Ross	2	3
Ebstan	2	6
AVSD	8	12
Rastelli	1	8

Nikaidoh/REV, biventricular outflow tract reconstruction; ASO, artery switch operation; IAA, interrupted aortic arch; TAPVC, total anomalous pulmonary venous connection; AVSD, atrioventricular septal defect.

Table 3. Patients' Characteristics and Surgical Data

	Group H (n = 63)	Group S (n = 55)
Age	5 d–6 yr	2 d–5 yr
Weight	12.8 ± 4.6 kg	10.6 ± 3.8 kg
Sex (male/female)	36/27	32/23
CPB time	237.5 ± 78.6	222.3 ± 47.6
Cross-clamping time	172.5 ± 66.4*	194.2 ± 38.5
Spontaneous defibrillation	58/63 (96.7%)*	40/55 (72.7%)

* Compared with group S; $p < 0.05$.

H= HTK

S = STH

Table 4. The Different Level of CK on Postoperative Days Between the Two Groups

	Postoperative Day 1	Postoperative Day 2
Group H	895.2 ± 345.4	542.5 ± 145.4*
Group S	1157.1 ± 428.6	864.1 ± 245.4

* Compared with group S; $p < 0.01$.

HTK vs STH: pediatric surgery

The major advantages of HTK solution:

- buffer effect enhances the efficiency of anaerobic glycolysis
- ketoglutarate acts as an intermediary in Krebs cycle and is a precursor of nicotinamide adenine dinucleotide (NAD)
- mannitol decreases cellular edcma
- **Kresh et al.** noted that protein buffers such as histidine might be superior to bicarbonate in stabilizing intracellular pH and the recovery of postischemic biochemical and mechanical parameters
- **del Nido et al.** demonstrated that the significant buffering capacity in a crystalloid solution can be effective in preserving myocardial adenosine triphosphate stores, improving postarrest contractile function, and minimizing myocardial necrosis

16. Kresh JY, Nastala C, Bianchi PC, *et al*: The relative buffering power of cardioplegic solutions. *J Thorac Cardiovasc Surg* 93: 309–311, 1987.
17. del Nido PJ, Wilson GJ, Mickle DA, *et al*: The role of cardioplegic solution buffering in myocardial protection. A biochemical and histopathological assessment. *J Thorac Cardiovasc Surg* 89: 689–699, 1985.

HTK vs STH: pediatric surgery

Liu et al. showed that:

- → doses of inotropic agent in the HTK group and in the St. Thomas group during the weaning of CPB were almost equal
- → spontaneous defibrillation occurred in more patients in the HTK group
- → The level of CK was always measured to evaluate the myocardium damage on postoperative days
- → The level of CK in all cases had increased markedly on the early post operative days, but CK in the HTK group was less than in group S (no significance) on postoperative day 1 and was significantly less than that in group S on postoperative day 2 ($p < 0.05$)

Conclusion:

- → The study showed the myocardium was damaged inevitably undergoing long-term complicated surgical procedures
- → HTK solution was more effective than the St. Thomas on the recovery of damaged myocardium

Discussion:

- → Hachida et al. indicated that promoting anaerobic glycolysis during ischemia by HTK results in superior prolonged preservation of the energetic and contractile functions of the heart
- → Takeuchi et al. also demonstrated that administration of histidine containing cardioplegia solution promotes anaerobic glycolysis and improves recovery of high-energy phosphates and contractile function in hypertrophied myocardium

SUMMARY

An optimal cardioplegia should have the following attributes:

(i) a rapid diastolic arrest

(ii) effective and definite myocardial protection

(iii) arrest should be readily and rapidly reversible

(iv) low toxicity

→ HTK solution meets all these criteria

Advantages of HTK:

- **single-dose perfusion**
- **long-term protection**
- **and low potassium concentration**