Forty years of glucose—insulin—potassium (GIK) in cardiac surgery: a review of randomized, controlled trials

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Summary

Glucose—insulin—potassium (GIK) solutions have been used in cardiac surgery for more than 40 years. At that time, membrane-polarizing and stabilizing effects on cardiomyocyte's action potential were regarded the main benefit. Two meta-analyses described methodological flaws in the early studies (e.g., case numbers, randomization principles, and levels of significance), and came to clearly different recommendations with regard to the usage of GIK in the therapy of acute myocardial function. During the 70s, as promising therapies for the treatment of AMI had become available (e.g., β-blockers and thrombolytic agents), the GIK technique was more widely introduced in cardiac surgery, e.g., during valve replacement. At present, 74 of 91 studies provide convincing evidence for the beneficial effects of insulin and/or GIK in cardiac surgery that go far beyond simple metabolic benefits and also include better recovery of myocardial tissue after ischemia. Yet, the exact underlying mechanisms remain still unknown. In this review article, two questions will be answered: why did GIK not become daily routine in cardiac surgery in spite of positive results from clinical studies, and does this technique merit more acceptance among the potential users? In view of the increasing number of older patients at higher risk, the demand for improving surgical procedures has renewed the interest in the GIK concept. The more recent literature suggests that the entire potential of GIK solutions has not been fully disclosed. A large single or multicenter trial with sound endpoints is mandatory.

Keywords: Cardioprotection; GIK mechanisms; Randomized trials; Endpoints

1. Introduction

Although the beneficial effects of glucose—insulin—potassium (GIK) infusion in the treatment of cardiac failure and its use in cardiac surgery have been described for more than 40 years, this technique is still a matter of controversy—even though a plethora of theoretical and clinical studies exists. In the early GIK research, the focus was placed on the management of acute myocardial infarction (AMI), where membrane-polarizing and stabilizing effects on cardiomyocyte's action potential were regarded the main benefit [1—5].

In two meta-analyses, methodological flaws in these early studies were identified, pertaining to case numbers, randomization principles, and significance levels [6,7]. For example, a widely regarded study from the British Medical Research Council [8] with a poor research design [9] resulted in an enormous impact among potential users, as it casted doubt on the benefit of GIK due to the official character of the authors and to the publication in a much valued journal.

Thus, it was no surprise that the above meta-analyses, although largely based on the same data, came to different recommendations with regard to the use of GIK in the therapy of acute myocardial infarction:

(1) the GIK therapy may have an important role in reducing the in-hospital mortality after AMI [6] and
(2) the routine use of GIK infusion in AMI patients is not recommended [7].

Both relatively negative results and the dawn of promising therapies for the treatment of AMI, such as β-blockers and thrombolytic agents, shifted the main interest during the 70s towards the use of GIK in cardiac surgery, and it was Braimbridge et al. [10] who, in 1969, described the use of GIK in the course of a triple Starr valve replacement. Several papers from other authors followed, predominantly demonstrating positive results with GIK infusions, as shown by a recent meta-analysis of all randomized studies using GIK in cardiac surgery [11].

Despite positive results from experimental studies, GIK did not obtain ample acceptance in the past. However, interest towards this technique has started to shift after the
positive effects of insulin on ischemic myocardium have been shown. These effects go far beyond a simple metabolic benefit; they include the better recovery of myocardial tissue after ischemia via still unknown mechanisms [12—14]. Even in cardiology, the discussion on the GIK use supportive to thrombolytic therapy after AMI was resumed, as a recent study provided evidence that a combined use of GIK and thrombolytic agents exerts positive effects on mortality [15]. However, most of the older studies were performed in the pre-thrombolytic era, and thus could not provide evidence for employing GIK plus thrombolysis that is routinely used in the treatment of AMI in the meantime. In consequence, the GIK technique was more widely introduced in cardiac surgery, e.g., during valve replacement and CABG.

In this review article, the following two questions will be answered: why did GIK not become daily routine in cardiac surgery in spite of predominantly positive results from clinical studies? Does this technique merit more acceptance among the potential users? This qualitative review article is also supposed to serve as an example, why good concepts do not become clinical standard in cardiac surgery.

2. Materials

A systematic search in several appropriate databases was performed: Medline, Pubmed, New England Journal of Medicine and Google to assess recent publications not yet contained in established databases.

The search algorithm was: glucose, insulin, potassium, GIK, cardiac surgery, and randomized controlled trial. The search covered the years between 1965 and June 2004. Some 200 citations were found, which were condensed to in-depth reviewed studies, i.e., which were rated in Medline with more than 50% relevance. Not included were also basic, theoretic, biochemical studies, case studies, in-vitro studies, and/or animal experimental studies. To possibly draw more concise conclusions, trials on diabetics, infants, or other specific patient groups were excluded, as well as studies on the use of GIK together with AMI, balloon catheterization, or other non-surgical interventions.

After strictly applying the above criteria, a total of 38 studies were identified by the end of June 2004. In addition, several reviews, comments, editorials, and other contributions were found.

3. Described mechanisms

In the beginning, energetic parameters were in the focus (e.g., see Refs. [16,17]), while in the more recent studies — acknowledging the energetic benefits — other beneficial effects were presented, such as growth factors, immune modulators, and cytokines. In most studies, however, one or a combination of GIK mechanisms was proposed. Six alternatives are listed below.

3.1. Membrane stabilization and anti-arrhythmic effects

Initially, electro-physiological effects, i.e., improved membrane polarization, were considered the main effect of GIK solution [1—5]. Presumably, insulin improves the potassium uptake of the myocyte [17,18], which causes a faster postoperative recovery to sinus rhythm [19].

In fact, GIK infusion significantly reduced the incidence of ventricular arrhythmia as well as of atrial fibrillation [20,21]. These protective effects are obviously important, since conduction abnormalities and postoperative arrhythmias are common complications after coronary bypass surgery [22]: atrial fibrillation has reportedly an incidence between 10% and 50% [23—25], most probably as a result of increased catecholamines after sympathetic activation [20,26]. A more recent study presents a typical contradictory example from within the GIK research, as it comes to the opposite conclusion, suggesting that GIK does not stabilize the cardiac rhythm at all but solely improves the glucose supply for cardiomyocytes [27].

3.2. Improved myocardial glycogen content

Preventive GIK supply prior to myocardial ischemia increases myocardial glycogen content, enabling prolonged synthesis of adenosine triphosphate and creatin triphosphate during anaerobic conditions [17]. Consequently, preoperative insulin application should improve both tolerance towards ischemia and recovery of contractile function [21,28—30]. It is mentioned that the exact underlying mechanism is still under discussion: Some authors submit the insulin-triggered, increased rate of glycogen turnover to be more important than the absolute cellular glycogen content, thus enabling faster and more effective supply of substrates for energy production [31,32].

As mentioned before, GIK was infused only during or even after ischemia in several studies (for review see Ref. [33]). Subsequently, patients would not benefit from increased energy stores.

3.3. Postoperative insulin resistance

Transient insulin resistance is one critical myocardial metabolic reaction following ischemia. It is part of a general hormonal stress response [13] and has reportedly a high potential for causing hyperglycemia [18]. Exogenous application of glucose as part of GIK infusion may further increase the blood glucose levels to values even above 250 mg/dl [18,33]. As a possible result, neurological injuries were described [34—38]. This risk, however, can be obviated by using individually administered, postoperative high-dose insulin [33].

3.4. Reduction of free fatty acids (FFA)

Peri- and postoperative myocardial ‘trauma-metabolism’ includes a neuroendocrine response with secondary metabolic effects [39]. Thus, the increased, stress-induced catecholamine release not only blocks the beneficial insulin effects but also induces a systemic lipolysis, which in turn leads to increased FFA levels with its negative consequences [40]: generation of free oxygen radicals, deteriorated efficiency of ATP-production with relatively high oxygen.
consumption compared to glucose oxidation [41], and membrane injury owing to high levels of acyl-carnitine [42,43].

All these consequences can be prevented by sufficient insulin, which inhibits the hormone-sensitive lipase of adipose tissues as well as activation of mitochondrial acetyl-CoA-carboxylase — thus directly inhibiting FFA oxidation.

3.5. Improved glucose utilization and contractile function

Beyond the well-known metabolic insulin effects, myocardial contractile function benefits directly from insulin-induced, increased expression of glucose transporters and improved turnover of Na—K—ATPases, mediating positive inotropic effects. Even in markedly injured cardiac tissue, high insulin doses (up to 1,200 IU) helped improving recovery of contractile function [16,44].

On the contrary, improved glycolysis under anaerobic conditions may alter intracellular lactate levels resulting in acidosis and cell damage [37,38,49].

3.6. Other effects of insulin and/or GIK

Some other effects of GIK infusions, that are not so consistently reported, also seem to play a role:

- improved anaplerosis of the Krebs cycle together with an increased supply of amino acids for protein synthesis [28,41,46],
- positive effects on synthesis of growth hormones and growth factors [12],
- improved cardiac output via vasodilation and lowering the total peripheral resistance [47—49],
- increased phagocytotic activity in neutrophile granulocytes resulting in lower infection risks and shorter recovery from surgery [13].

It is worth mentioning that several of the positive GIK effects are not yet fully understood. Despite the various starting points, methods, and study designs, a majority of studies draws positive conclusions with regard to the GIK effects, leaving room for the assumption that up to now, unknown, non-metabolic, positive inotropic effects of insulin exist [14,33].

The uncertainty about the underlying mechanisms in an era of evidence-based decisions is one of the reasons preventing a major breakthrough of GIK solutions. The publication of new approaches on a near-monthly basis does not help to substantiate the facts.

4. Research design

A closer look at the methods and the study design reveals a variety of unacceptable technical flaws, making the results of several studies questionable. Examples are listed and discussed below: small number of cases, recruitment and randomization of test groups and control groups, varying duration and routines of operation, different application of GIK infusion, different measures to evaluate the GIK effects. Different research designs are summarized in Table 1.

4.1. Case numbers

Most studies had a sample size < 20 in the test group and the control group. Nine [12,39,50–56] of the 38 studies comprised even 10 or less patients in one of the two groups. Obviously, individual physiological reactions of a single patient can already induce a substantial error within such small samples. It should be taken into consideration that for studies with relevant results, e.g., comparison of post-operative mortality rates, sample sizes of 2 × 500 are required [57]. This requirement is not nearly met by any of the studies.

The only two trials that report on relatively large samples (Hynninen et al. [22]: 243/258 patients; Groban et al. [27]: 188/193 patients) do not contribute to a better understanding of specific GIK mechanisms as both studies concentrate on the effects of insulin on postoperative arrhythmias. While in the first study, only very low-dose insulin (10 IU/l) was administered [22], the conclusions drawn from the latter study might be biased, as the trial was not randomized [27].

4.2. Recruitment of groups and randomization

Details on randomization principles are only given in a small number of studies, and the details on how patients were recruited are frequently obscure. Some examples are provided as follows.

No details on gender are presented, the age range is considerable (mean: 51 years; range: 33–72 years), and details on exclusion criteria are missing [56]. Similarly, no details on gender are given. The average age is not presented for the cohort with a large range in age (41–74 years). In addition, the size of both groups is not presented and again, exclusion criteria are missing [53]. Sixteen patients were included in another study. They were assigned to three groups (5/5/6). Without further explanation, only ‘emergency patients’ were excluded from this retrospective study [50]. The risks in the GIK group (n = 19) and in the control group (n = 20) were different in a further study [58]. Whereas the ejection fraction was below 45% in 47% of the GIK group, EF was low in only 15% in the control group, making the comparison between different interventions difficult. Three other examples document flaws of other studies and in consequence, the difficulties in their interpretation. In one study, the sample size was seemingly unbalanced (9 GIK patients vs 22 control patients). Moreover, details on the age were missing, and the medical history, such as prior chest pain and infarctions, was only poorly presented [54]. Another study reports on surprisingly young patients (mean age: 38 years) who were mostly females (mean age: 35 years) [59]. Thus, this study includes patients who are not representative for open heart surgery. In a last study on 20 patients, six of them needed to be excluded retrospectively due to technical problems with measuring the ejection fraction via TC-99m-scintigraphy. Hence, any randomized assignment to the GIK group and the control group seems questionable [51].
4.3. Surgical procedures

Ischemia during cardiopulmonary bypass (CPB) and/or aortic cross-clamping (ACC) as well as components and temperature of cardioplegic solutions will greatly affect protection via GIK infusion. These parameters were very different between the individual studies and between the GIK group and control group, even within one single study. In six of the studies, no information was provided at all on the duration of either CPB or ACC [32,33,53,60—62]. In other studies, CPB lasted from 70 ± 20 min [58] to 159 ± 4 min [49] in the control group, 27 min [54] in the GIK group, and ACC lasted 128 ± 42 min in the control group [50]. Thus, the duration of the procedures differed by a factor of almost four.

Cardioplegic regimens were also very different among the studies: cold blood cardioplegia was predominantly employed; however, warm blood cardioplegia [63] and crystalloid cardioplegic solutions were also used. Even within the same study, different cardioplegic regimens were used in the GIK group and the control group, with no mention as to how this difference could have contributed to the results [12].

4.4. Application protocols

Insulin dosages and application protocols were extremely different, i.e., the insulin dosage varied by a factor of 100 among the studies, preventing meaningful comparison of GIK infusion. Details of differences with respect to dosages and protocols were thoroughly discussed more recently (for review see Ref. [11]). The same authors have additionally developed a high-dose application protocol for insulin [33].

4.5. Measures

Measures to evaluate the effects of GIK infusion vary considerably among the studies. Some of them are listed below; they were used either alone or in combination with other measures. Physiologic measures comprised ventricular function, oxygen extraction and/or pressures in the pulmonary circuit. Yet, 21 of the 38 studies assessed the effects of GIK infusion without measuring the pre- and postoperative cardiac index, which is considered an important measure to compare the effects of different procedures.

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Sample size</th>
<th>Insulin dosage</th>
<th>GIK application</th>
<th>Measures/ endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>Haider, Coraim [16]</td>
<td>10</td>
<td>10</td>
<td>1.0 IU kg/h for 30 min</td>
<td>Preoperative - x - I CK-MB - Trop I Others</td>
</tr>
<tr>
<td>1991</td>
<td>Haider, Benzer [18]</td>
<td>12</td>
<td>10</td>
<td>400 IU/day</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1992</td>
<td>Haider, Schütz [17]</td>
<td>11</td>
<td>11</td>
<td>1.0 IU (kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1993</td>
<td>Satler et al. [56]</td>
<td>10</td>
<td>7</td>
<td>1.5 ml/(kg h): 50 IU</td>
<td>n.a. n.a. n.a. n.a.</td>
</tr>
<tr>
<td>1993</td>
<td>Boldt, Knothe [35]</td>
<td>7</td>
<td>7</td>
<td>1.35 IU/(kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1993</td>
<td>Brodin et al. [51]</td>
<td>7</td>
<td>7</td>
<td>1.0 IU/(kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1993</td>
<td>Hachida et al. [70]</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1995</td>
<td>Wistbacka et al. [69]</td>
<td>20</td>
<td>20</td>
<td>0.12 IU/(kg h)</td>
<td>n.a. n.a. n.a. n.a.</td>
</tr>
<tr>
<td>1995</td>
<td>Svedjeholm, Huljebrand [25]</td>
<td>16</td>
<td>-</td>
<td>Bolus 25 IU, then 1.0 IU/kg</td>
<td>n.a. n.a. n.a. n.a.</td>
</tr>
<tr>
<td>1995</td>
<td>Rudez et al. [66]</td>
<td>10</td>
<td>10</td>
<td>1.0 ml/(kg h): 120 IU</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1996</td>
<td>Rydell et al. [67]</td>
<td>11</td>
<td>11</td>
<td>1.0 ml/(kg h): 80 IU</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1996</td>
<td>Coleman et al. [68]</td>
<td>22</td>
<td>22</td>
<td>0.8—1.2 ml/(kg h): 100 IU</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1996</td>
<td>Oldfield, Commerford [21]</td>
<td>9</td>
<td>9</td>
<td>10 IU/kg</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1997</td>
<td>Lazar et al. [46]</td>
<td>15</td>
<td>15</td>
<td>1.0 ml/(kg h): 50 IU</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1999</td>
<td>Besogul et al. [59]</td>
<td>15</td>
<td>15</td>
<td>1.0 IU kg/h</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>1999</td>
<td>Solberg et al. [62]</td>
<td>28/64/132</td>
<td>1 ml/(kg h): 80 IU</td>
<td>- x - x - x - x - x - x - x - x</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Lindholm et al. [65]</td>
<td>11</td>
<td>11</td>
<td>Bolus 100 IU, then 250 IU</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2000</td>
<td>Kjellman et al. [57]</td>
<td>13</td>
<td>15</td>
<td>Bolus 1.0 IU/kg, then 4.0 IU/(kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2000</td>
<td>Rao et al. [63]</td>
<td>12/17</td>
<td>10/17</td>
<td>10 IU/l</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2000</td>
<td>Lindholm et al. [49]</td>
<td>16</td>
<td>14</td>
<td>Bolus 600 IU, then 600 IU/h</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2000</td>
<td>Hakimian, Borger [22]</td>
<td>243</td>
<td>258</td>
<td>10 IU/l</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2000</td>
<td>Leil et al. [60]</td>
<td>21</td>
<td>20</td>
<td>1.5 ml/(kg h): 50 IU</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2001</td>
<td>Rudez et al. [66]</td>
<td>19</td>
<td>20</td>
<td>0.75 IU/(kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2001</td>
<td>Groban, Butterworth [27]</td>
<td>188</td>
<td>193</td>
<td>Bolus 25 IU, then 1.0 IU/kg</td>
<td>Insulin application follows blood glucose</td>
</tr>
<tr>
<td>2001</td>
<td>Rusilas et al. [13]</td>
<td>15</td>
<td>15</td>
<td>16.3 ± 2.2 IU</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2001</td>
<td>Smith et al. [68]</td>
<td>22</td>
<td>22</td>
<td>Insulin application follows free fatty acids</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2001</td>
<td>Takeuchi et al. [50]</td>
<td>6</td>
<td>5/5</td>
<td>10 IU/l</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2001</td>
<td>Doenst, Bothe [33]</td>
<td>27 (3 groups)</td>
<td>-</td>
<td>Insulin application follows blood glucose</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2002</td>
<td>Szabo et al. [64]</td>
<td>89</td>
<td>-</td>
<td>Variable, up to 1.0 IU/(kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2002</td>
<td>Walker, Quinn [37]</td>
<td>60</td>
<td>68</td>
<td>70 IU/l</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2002</td>
<td>Wallin et al. [12]</td>
<td>9</td>
<td>9</td>
<td>1.0 IU kg/h, decreasing to 0.1 IU</td>
<td>- x - x - x - x - x - x - x - x</td>
</tr>
<tr>
<td>2003</td>
<td>El-Zahaby et al. [64]</td>
<td>89</td>
<td>-</td>
<td>Variable, up to 1.0 IU/(kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
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<tr>
<td>2003</td>
<td>El-Zahaby et al. [64]</td>
<td>89</td>
<td>-</td>
<td>Variable, up to 1.0 IU/(kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
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<tr>
<td>2003</td>
<td>El-Zahaby et al. [64]</td>
<td>89</td>
<td>-</td>
<td>Variable, up to 1.0 IU/(kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
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<tr>
<td>2003</td>
<td>El-Zahaby et al. [64]</td>
<td>89</td>
<td>-</td>
<td>Variable, up to 1.0 IU/(kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
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<tr>
<td>2003</td>
<td>El-Zahaby et al. [64]</td>
<td>89</td>
<td>-</td>
<td>Variable, up to 1.0 IU/(kg h)</td>
<td>- x - x - x - x - x - x - x - x</td>
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</tbody>
</table>
As well, electrocardiographic measures were used. The clinical laboratory analyzed markers of myocardial injury only in seven studies from blood status, substrates, hormones, growth factors, markers of inflammation [12], and immune modulators [49]. Other objective measures were derived from biopsies, i.e., from intracellular glycogen content, cAMP, ATP, as well as from phagocytotic activity. Unfortunately, also less stringent criteria, such as time on the ICU, duration of intubation or need for inotropic support were used to compare the two procedures. These latter measures, however, depend to a great extent on subjective judgments. Moreover, weight loss or intra- and postoperative mortality were used as data that are less biased.

5. Summary and conclusions

Studies on the effects of GIK infusion in the last four decades are extremely heterogeneous and can only be compared with difficulties. Several of them are based on a low number of cases and often leave questions unanswered with respect to design and methods.

Twenty-five of the 38 studies report positive results with regard to GIK infusions [12, 16–18, 21, 26, 32–34, 37–39, 46, 49, 51, 53–57, 59, 63–67], 11 studies report neutral or negative results [13, 22, 27, 35, 52, 58, 60, 61, 68–70], and two studies [50, 62] argue neither for nor against GIK infusions, as both studies were primarily not aimed at GIK effects but on other endpoints.

Three studies reporting neutral or negative results were performed on patients undergoing off-pump surgery. Due to the nature of this operation technique, it is questionable, whether GIK can exert beneficial effects in patients without myocardial infarction at all [60]. After excluding these three studies and the two studies that were not aimed at GIK effects, the ‘positive ratio’ rises from 66% to 76% (25 of 33) which is in symphony with the results of other papers, e.g., Bothe and coworkers [33].

In summary, we cannot provide answers to our two earlier questions.

(1) Although the majority of studies come to a positive conclusion and recommend the use of GIK infusion in cardiac surgery, mechanisms of action for the beneficial effects as well as adequate measures for their assessment are still being discussed. Thus, none of the studies alone provide enough evidence for an ample use of GIK. However, a clear trend in favor of its use exists among the majority of studies.

Due to the inconclusive and unsatisfying situation, GIK has not become part of daily clinical routine — especially in light of today’s standards in evidence-based decision-making. After 40 years of research, the concept may have lost part of its initial attractiveness.

(2) In view of the increasing number of older patients at higher risk, the demand to further improve the outcome of cardiac surgery has renewed the interest in the GIK concept. The more recent evidence suggests that the entire potential of the GIK solution has not yet been fully disclosed. A large single or multicenter trial with sound endpoints is mandatory.

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