Helicobacter pylori in the critically ill patient
van der Voort, P.H.J.

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Chapter 3

Upper gastrointestinal bleeding after cardiac surgery: Is specific prophylaxis in routine bypass procedures needed?

P.H.J. van der Voort¹ and D.F. Zandstra²

¹ Dept. of intensive care, Medisch Centrum Leeuwarden-Zuid, Leeuwarden
² Dept. of intensive care, Onze Lieve Vrouwe Gasthuis, Amsterdam

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Abstract

Objectives: To review the literature concerning pathogenesis and incidence of stress ulceration (SU) in patients undergoing cardiac surgery. To determine which methods are useful in the prevention of SU and to analyse whether SU prophylaxis by acid reduction is effective in patients undergoing cardiac surgery.

Design: Literature review from Medline and reference list of identified articles until 1998.

Measurements and main results: SU in patients after cardiac surgery are reported since 1957. All papers are retrospective reports. Controlled clinical trials concerning SU prophylaxis have not been performed. Definition of lesions and bleeding are variable. The overall incidence of upper gastrointestinal bleeding (UGIB) was 0.45% (505 bleedings out of 113323 patients). In patients with known use of SU prophylaxis with histamine receptor antagonists or antacids the incidence of UGIB was 0.35% and in patients without this medication the incidence of UGIB was 0.51% (p=0.16). Ischaemia, reperfusion and endotoxaemia are the main pathogenetic mechanisms in SU formation. Valve replacement, aortic cross clamping and bypass time, non-pulsatile flow during bypass, re-operation and inflammatory state are risk factors for UGIB.

Conclusions: Risk factors for UGIB are analysed. Reviewing the literature, the incidence of UGIB in patients after cardiac surgery was not significantly lower in patients using pharmacological stress ulcer prophylaxis compared to patients without this medication. This finding and the lack of controlled clinical trials concerning the prophylaxis of SU in patients after cardiac surgery should withhold physicians to use SU prophylaxis by antacids or histamine receptor antagonists routinely.

Introduction

In 1957 Berkowitz was the first to report “acute peptic ulceration following cardiac surgery” [1]. These stress ulcerations are the most frequent abdominal complication seen after cardiopulmonary bypass procedures amongst others as pancreatitis, cholecystitis and ischaemic intestines. In general intensive care patients stress ulceration prevalence reaches 82% when patients are endoscoped routinely [2]. Stress ulcer related bleeding is less common, occurring in 0.6 to 9% of general intensive care patients [3-7]. The incidence of upper gastrointestinal bleeding (UGIB) in patients undergoing cardiac surgery is not prospectively investigated. However, according to stress ulcer prophylaxis in general intensive care patients cytoprotective
agents or acid suppressing agents are being used in some clinics to prevent
UGIB after cardiac surgery [3]. The routine use of cytoprotective or acid sup­
pressive agents may have considerable impact on health care resources
because of the great number of cardio pulmonary bypass (CPB) procedures
nowadays. In this literature study we review the available literature concern­
ing the incidence, pathogenesis and prevention of stress ulceration and
UGIB after CPB procedures for cardiac surgery. We compare the inciden­
ce of UGIB in patients undergoing cardiac surgery with and without specific
pharmacologic prophylaxis with acid suppressive agents.

**Methods**

Full papers and abstracts are included for analyses when the incidence of
UGIB in patients is reported. Studies are collected by searching Medline for
the key words: stress ulcer, cardiac surgery, bypass surgery, upper gast­
rointestinal bleeding, gastrointestinal complication. In addition, reference
lists from identified articles are searched for other studies which may be
included. Studies that reported perforated ulcers which needed surgical
intervention but which did not identify UGIB were excluded.

**Statistical analysis**

A comparison of groups was performed by the Pearson's Chi Square test.
The statistical analysis was made with the SPSS statistical analyser relea­
se 8.0.0 (SPSS inc., USA, 1997). A p value < 0.05 was considered to be sta­
tistically significant.

**Results**

25 studies were included for review and are summarised in table 1. All stu­
dies are retrospective reports of identified upper gastro-intestinal bleedings.

**Definitions**

Stress ulceration can only be detected by upper gastrointestinal endoscopy.
However, most studies do not report consequent endoscopies in case of
UGIB. UGIB may also be due to other causes than stress ulceration, for
instance oesophagitis, variceal bleeding or tumours. Therefore the true inci­
dence of stress ulceration as the cause of bleeding remains unknown. Even
endoscopic studies are difficult to compare because stress ulcers are not
uniformly defined in clinical studies. Mucosal damage in critically ill and sur­
gical patients can be found in several stages. In a study of gastric mucosal
lesions after severe head injury Brown [8] used a scale of mucosal damage
### Table 1

Incidence of upper gastrointestinal bleeding in 25 studies since 1969.

<table>
<thead>
<tr>
<th>Author of the study</th>
<th>Nr. of patients</th>
<th>Nr. of bleedings</th>
<th>UGIB Incidence%</th>
<th>Mortality %</th>
<th>Prophylaxis</th>
<th>Definition of bleeding of SU</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams 1965 [49]</td>
<td>150</td>
<td>3</td>
<td>2.0</td>
<td>ND</td>
<td>No</td>
<td>Melena</td>
<td>ND</td>
</tr>
<tr>
<td>Loop 1967-1970 [50]</td>
<td>741</td>
<td>9</td>
<td>1.2</td>
<td>23.7</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Loop 1972 [50]</td>
<td>1000</td>
<td>26</td>
<td>2.6</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Loop 1975 [50]</td>
<td>1000</td>
<td>3</td>
<td>0.3</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Loop 1978 [50]</td>
<td>1000</td>
<td>0</td>
<td>0.0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Katz 1972‡ [12]</td>
<td>100</td>
<td>11</td>
<td>11</td>
<td>ND</td>
<td>†</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Welsh 1973 [16]</td>
<td>7333</td>
<td>16</td>
<td>0.22</td>
<td>81</td>
<td>No</td>
<td>†</td>
<td>ND</td>
</tr>
<tr>
<td>Taylor 1973 [14]</td>
<td>&gt;5000</td>
<td>38</td>
<td>&lt;0.76</td>
<td>23.6</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Panzer 1979 [51]</td>
<td>512</td>
<td>8</td>
<td>1.3</td>
<td>13</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Chigot 1981 [52]</td>
<td>7847</td>
<td>9</td>
<td>0.11</td>
<td>ND</td>
<td>Antacids</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Hanks 1982 [21]</td>
<td>5080</td>
<td>19</td>
<td>0.37</td>
<td>63</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Pinson 1983 [20]</td>
<td>5682</td>
<td>6</td>
<td>0.11</td>
<td>67</td>
<td>No</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Jones 1983 [39]</td>
<td>7221</td>
<td>19</td>
<td>0.26</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Moneta 1985 [53]</td>
<td>1663</td>
<td>9</td>
<td>0.5</td>
<td>ND</td>
<td>ND</td>
<td>†</td>
<td>ND</td>
</tr>
<tr>
<td>Leitman 1987 [15]</td>
<td>6452</td>
<td>20</td>
<td>0.31</td>
<td>45</td>
<td>Ant/H₂RA</td>
<td>†</td>
<td>ND</td>
</tr>
<tr>
<td>Heikkinnen 1987 [19]</td>
<td>1688</td>
<td>17</td>
<td>1.0</td>
<td>53</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Krasna 1988 [40]</td>
<td>1279</td>
<td>6</td>
<td>0.47</td>
<td>33</td>
<td>Ant/H₂RA</td>
<td>†</td>
<td>Endoscopy</td>
</tr>
<tr>
<td>Widera 1990 [54]</td>
<td>2161</td>
<td>13</td>
<td>0.6</td>
<td>24</td>
<td>ND</td>
<td>†</td>
<td>Endoscopy</td>
</tr>
<tr>
<td>Lebovics 1991 [18]</td>
<td>4892</td>
<td>18</td>
<td>0.37</td>
<td>11</td>
<td>56%</td>
<td>†</td>
<td>Endoscopy</td>
</tr>
<tr>
<td>Huddy 1991 [38]</td>
<td>4473</td>
<td>20</td>
<td>0.45</td>
<td>45</td>
<td>No</td>
<td>†</td>
<td>ND</td>
</tr>
<tr>
<td>Ohri 1991 [17]</td>
<td>4629</td>
<td>20</td>
<td>0.43</td>
<td>20</td>
<td>No</td>
<td>ND</td>
<td>Endoscopy</td>
</tr>
<tr>
<td>Christenson 1994 [22]</td>
<td>3129</td>
<td>11</td>
<td>0.35</td>
<td>0</td>
<td>Ant/H₂RA</td>
<td>†</td>
<td>ND</td>
</tr>
<tr>
<td>Tsioos 1994 [37]</td>
<td>19246</td>
<td>44</td>
<td>0.23</td>
<td>20</td>
<td>H₂RA</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Mercado 1994 [55]</td>
<td>4223</td>
<td>26</td>
<td>0.51</td>
<td>16</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Yilmaz 1996 [56]</td>
<td>3158</td>
<td>25</td>
<td>0.7</td>
<td>90</td>
<td>No</td>
<td>†</td>
<td>ND</td>
</tr>
<tr>
<td>Pollard 1996 [13]</td>
<td>9476</td>
<td>38</td>
<td>0.40</td>
<td>31</td>
<td>89%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Halm 1996 [42]</td>
<td>2950</td>
<td>26</td>
<td>0.88</td>
<td>ND</td>
<td>H₂RA/Sucr</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Total</td>
<td>113323</td>
<td>505</td>
<td>0.45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definition</th>
<th>Diagnosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>H; positive faecal blood test and decrease in haemoglobin.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>†; hematemesis and/or melena and decrease in haemoglobin or hypotension.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*; Confirmed GI bleeding site and need for transfusion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‡; only aortic valve replacements.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ND; not defined.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂RA; histamine₂-receptor antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ant; antacids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucr; sucralfate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
which resembles the Lanza score which is used to define NSAID related mucosal damage [9]. In the Brown classification petechiae are intra-mucosal haemorrhages without mucosal breaks. The Lanza classification does not define petechiae but erosions are counted. Erosions are defined as white based breaks in the mucosa with no observable depth and an ulceration is a large mucosal break (> 0.5 cm) with observable depth. In 17 out of the 25 studies that are summarised in table 1 the definition of bleeding is not clearly defined. Other definitions have been used as indicated in the table.

Epidemiology

In 1987 Munakata [10] performed a prospective endoscopic study in twenty patients who underwent open heart surgery. The patients were endoscoped before, just after and 3 days after the operation. In 88\% of the patients some form of acute gastric mucosal damage was found within 3 days after the procedure but upper gastrointestinal bleeding was not observed. He also found a decreased gastric acid production during and after surgery and concluded that gastric acid is probably not involved in the pathogenesis of these lesions. This is the only study that prospectively endoscoped patients undergoing cardiac surgery for mucosal injury. Table 1 summarises the studies that address the incidence of gastrointestinal bleeding in patients undergoing cardiac surgery, ranging from 0 to 22\%. Taken together 113323 procedures led to 505 bleedings of the upper gastrointestinal tract (0.45\%).

The report of Mead in 1969 [11] is a short communication lacking detailed information about the patients and the diagnostic methods. The extremely high UGIB incidence of 22\% fell to 1.9\% after the start of the routine use of antacids. The study was not a prospective placebo controlled clinical trial and should not be the guideline for stress ulcer prophylaxis in patients undergoing cardiac surgery. No other studies have been performed that compare patients with or without routine use of stress ulcer prophylaxis. The second highest incidence of UGIB was found in the study from Katz in 1972 [12]. In a retrospective analysis of a group of patients operated around 1965 the incidence of UGIB appeared to be 11\%. The technical advances that have been made since make these patients difficult to compare with patients operated today. All studies since the 1980’s show a UGIB incidence around 0.5\%. These studies are retrospective analysis and it may be possible that some cases of UGIB were not detected and therefore underestimate the true incidence.

Endoscopy in patients with gastro-intestinal bleeding show a variable location of the ulcers. The prospective endoscopic study from Munakata found a predominant corporeal location of the gastric lesions but these lesions did not bleed [10]. In the study of Pollard [13] the source of bleeding was gastri-
tis in 70% and solitary ulcers in 17.5%. Taylor [14] found 10 multiple ulcers (8 gastric), 8 single ulcers (7 duodenal), 7 gastroduodenitis, 1 jejunitis. Leitman [15] found in 18 out of 20 patients a gastroduodenal origin of bleeding and in 2 a bleeding site distal from the Treitz ligament. Welsh [16] found in 9 patients that the origin of bleeding was an oesophageal varix in 1 patient, multiple gastric lesions in 1, multiple gastric and duodenal ulcers in 3, pre-pyloric ulcer in 1, ulceration of the esophagogastric junction in 1 and haemorrhagic enteropathy in 2. Ohri [17] found the site of bleeding in 5 patients to be the stomach and the duodenum in 6; Lebovic [18] found 16 duodenal ulcers, 4 erosive gastritis and 2 gastric ulcer. No predominant site (stomach or duodenum) can be extracted from these data but frequently the bleedings appeared not to be caused by stress ulceration.

Heikkinen [19] found that the onset of bleeding was 11.1 +/- 6.7 days after the operation. In most patients this accompanied a multiple organ failure. Hinson [20] separated early and late general surgical complications after cardiopulmonary bypass surgery. Of the gastroduodenal complications 6 early (within 6 weeks after the operation) and 7 late (more than 6 weeks after the operation) complications were found in 5682 cardio-surgical patients. Hanks [21] found the incidence of bleeding 20.2 +/- 13.3 days after the operation. Taylor [14] found that 16 patients bled within the first 5 days after the operation, 17 after 6 to 10 days and 5 patients between the 11th and the 27th day. Welsh [16] found in 16 patients that the onset of bleeding was within 2 weeks in 12 and after 2 weeks in 4 patients. In the study of Christenson [22] all UGIB occurred within 8 days after the operation. Thus, the bleedings appear to be equally spread over time. With regard to the onset of bleeding the pathogenesis may be different. Early bleedings may be related to acute haemodynamic disturbances due to hypovolaemia or low cardiac output. Late onset (more than 7 days after surgery) bleedings are in many cases related to focal infections which induce a hyperinflammatory status with microcirculatory disturbances and defective mucosal oxygenation ultimately leading to stress ulceration [23].

Pathophysiology
The pathogenesis of stress-ulceration is complex and multifactorial [24]. The most important mechanisms which are involved in patients undergoing cardiac surgery are summarised.

Ischaemia
Reduced splanchnic and gastric bloodflow lead to decreased oxygen delivery and energy deficit. In this ischaemic situation the barrier function of the mucosa decreases and back diffusion of acid may occur, leading to mucosal damage and erosions or ulcers. A reduced splanchnic blood flow in
patients undergoing cardiac surgery may be caused by hypovolaemia, low cardiac output or vasoconstrictive medications. Many patients appear to be hypovolaemic at the time of elective surgery. In the study of Christenson [22] hypovolaemia was a risk factor for gastro-intestinal complications with a relative risk of 1.76 in a multivariate analysis. In piglets who were bled to a decrease in blood volume of 40% gastric ulcerations were found in the most ischaemic parts of the stomach [25]. Optimalisation of intravascular volume prior to and during surgery for femoral fractures improves mortality and shortens hospital stay [26]. On the other hand, when splanchnic vasoconstriction is present due to hypovolaemia it takes hours after adequate volume replacement before vasoconstriction resolves [27]. Anaesthesia may lead to spasm of the muscularis mucosae in guinea pigs [28]. The spasms continued for hours and led to full thickness necrosis of the mucosa. During cardio-pulmonary bypass gastric mucosal oxygen delivery decreases which will lead to gastric mucosal acidosis and increased intestinal permeability. Increasing systemic DO₂ by increasing pump flow rate did not correct this [29]. Thus anaesthesia, cardio-pulmonary bypass, vasoconstrictive medication and hypovolaemia all lead to ischaemia and contribute to the formation of stress ulceration.

Reperfusion
During ischaemia the levels of gastric mucosal adenosine triphosphate (ATP) are reduced. ATP breakdown in ischaemic tissue leads to hypoxanthine. In ischaemic tissue xanthine dehydrogenase is converted to xanthine oxidase. When reperfusion occurs oxygen combines with hypoxanthine, in a reaction that is catalysed by xanthine oxidase, to form superoxide radicals. These superoxide radicals are scavenged by superoxide dismutase. Allopurinol inhibits xanthine oxidase and thereby decreases the formation of superoxide radicals. In baboons gastric ischaemia and reperfusion produced gastric stress lesions that could be completely prevented by allopurinol and superoxide dismutase [30].

Endotoxins and Inflammatory response
Increased intestinal permeability after cardiac surgery correlates with the degree of endotoxaemia [31]. The degree of endotoxaemia is related to the use of ephedrine especially during hypovolaemia. Endotoxaemia may lead to vasoconstriction. Also cellular function is impaired by endotoxins characterised by mitochondrial swelling and disruption of inner structure leading to mucosal damage [32]. Patients with higher levels of endotoxin have higher levels of TNF and IL-6 and more often a post-perfusion syndrome. TNF and IL-6 increase the expression of adhesion molecules on endothelium and on the leukocyte [33]. Leukocyte adhesion and impairment of micro-circulation will occur and lead to mucosal damage. TNF, IL-6 and endotoxin levels were
significantly lower in patients who were effectively decontaminated by selective decontamination of the digestive tract prior to cardiopulmonary bypass surgery [34]. The presence of pneumonia, and thus an enhanced inflammatory state, correlates with the occurrence of gastro-intestinal bleeding after cardiac surgery [13].

**Gastric acid**

Although Munaka [10] did not find a relation between gastric acid secretion and stress ulceration in patients after cardiac surgery it is known that mucosal injury leads to back diffusion of acid and further damage. Martin [35] showed that failure to control intragastric pH was associated with gastro-intestinal bleeding in septic patients. In a meta-analysis it was shown that histamine₂-receptor antagonists were effective in preventing clinically important gastro-intestinal bleeding in general intensive care patients [36]. More doubt consists about sucralfate [3,36]. Neither prospective nor retrospective controlled studies have been performed in patients undergoing cardiac surgery to investigate a preventive role of acid suppression on stress ulceration.

**Risk factors**

A few studies summarised in table 1 have made an analysis of risk factors. The most important risk factors will be discussed here.

**Pre-operative condition**

Ageing is a risk factor for the development of gastro-intestinal complications [22,37], but not all studies found a significant correlation [38]. In a multivariate analysis hypertension, heart failure defined by New York Heart Association class III and IV and a left ventricular ejection fraction of less than 40% were the strongest risk factors [22]. Renal failure (urea greater than 20 mmol/l) was a significant risk factor for gastro-intestinal complications after cardiac surgery but respiratory failure was not [38].

**History of ulcer disease**

Patients with a history of peptic ulcer disease were more at risk for UGIB after cardiac surgery than patients without previous peptic ulcer disease [12,16,18]. However, Hanks found only 1 patient with previous ulcer out of 19 patients with UGIB after cardiac surgery [21]. Heikkinen did not find a correlation between a previous ulcer history and postoperative bleeding [19].

**Aortic cross-clamping and cardio-pulmonary bypass time**

Several studies found that cardiopulmonary bypass time and not aortic cross clamping time was significantly longer in patients who suffered from UGIB after cardiac surgery compared to patients who did not have UGIB [15-17,19,39] but other studies did not find this relationship [12, 22,40].
Valve replacement and anticoagulant therapy
All studies that included patients with aortic and mitral valve replacement found an increase in UGIB compared to patients undergoing coronary artery bypass surgery. Patients with aortic stenosis are known to have arteriovenous malformations with associated intestinal bleeding which is unrelated to surgery but may bleed more often after surgery due to anticoagulant therapy. Heikkinen found that 24% of the bleedings occurred after excessive administration of anticoagulants [19]. There was no difference in bleeding incidence between patients using warfarin or aspirin with dipyridamol.

Normothermia or hypothermia
Two studies address this issue. Christenson did not find a difference in abdominal complications (most often gastro-intestinal bleeding) [22]. In 1787 patients who were operated under hypothermia 41 had abdominal complications and in 1269 patients with normothermic cardiopulmonary bypass 32 had abdominal complications (not specified). Huddy did not find significant differences between patients below 20°C, 21-30°C, 31-36°C or 37°C [38]. These findings are in concordance with the fact that gastric mucosal pH during pulmonary bypass did not differ in patients at 30°C or 35°C [41].

Re-operation, emergence operation and re-exploration
Re-exploration for postoperative complications is a risk factor for the development of gastro-intestinal bleeding in several studies [12,15,16]. Post-operative complications as tamponade or bleeding will lead to shock, vasoconstriction of the splanchnic vessels and therefore ischaemia. Emergency operation in patients in cardiogenic shock and therefore mucosal ischaemia more often lead to gastro-intestinal bleeding [15]. Christenson found a relative risk of 1.03 for emergence operation in a multivariate analysis [22]. The relative risk for re-operation was 1.38.

Pulsatile versus non-pulsatile flow
In the study of Huddy half of the patients received pulsatile flow cardiopulmonary bypass but only 8 out of the 35 gastro-intestinal complications occurred in this group (p<0.001) [38]. No other clinical studies addresses this issue but endotoxin, TNF and IL-6 levels were lower and a better gastric pH was present in patients who were operated with pulsatile flow compared to non-pulsatile flow [34].

Intra-aortic balloon pump (IABP)
The use of IABP was highly significantly correlated with the occurrence of gastro-intestinal complications in one study (p<0.003) [37]. Whether the IABP itself or the cardiogenic shock for which it is usually instituted leads to gastro-intestinal bleeding is not clear from this study.

Pneumonia
We stated before that an inflammatory state is a risk factor for gastro-intes-
tinal bleeding. In the study of Pollard 26% of the patients with gastro-intestinal bled had a pneumonia at that time [13].

*Helicobacter pylori*

It was hypothesised for the first time by Ellison in 1996 that gastric mucosa with inflammation caused by infection with *H. pylori* is more prone to ischaemic damage than gastric mucosal without infection [6]. The only study that addresses this question in patients after cardiac surgery is from Halm [42]. *H. pylori* antibodies were found in 77% of the 26 patients who had upper gastro-intestinal bleeding after cardiac surgery compared to 63% in a control group of hospitalised patients (p=0.16). However, serology frequently results in a false negative test in patients after cardiac surgery due to blood loss and haemodilution [43]. Therefore the prevalence of *H. pylori* in patients after cardiac surgery is probably higher. More studies on this topic need to be done.

**Pharmacological prophylaxis**

Placebo controlled studies concerning stress ulcer prophylaxis in post-operative bypass surgery patients have not been performed. A survey in the Netherlands showed that 2 out of the 12 centres for cardiac surgery used stress ulcer prophylaxis routinely despite the lack of any evidence concerning effectiveness and efficiency. In one centre ranitidine was used, in the other antacids. We compared studies from table 1 using stress ulcer prophylaxis with the studies not using stress ulcer prophylaxis. It is shown in table 2 that in 47868 patients with stress ulcer prophylaxis 169 UGIB occurred (0.35%). In 25609 patients without prophylaxis 130 UGIB occurred (0.51%). This difference does not reach significance (p=0.16).

**Table 2**

Upper gastrointestinal bleeding in patients with and without stress ulcer (SU) prophylaxis by histamine₂-receptor antagonists or antacids.

<table>
<thead>
<tr>
<th>Nr. of procedures</th>
<th>Nr. of bleedings</th>
<th>% of bleedings</th>
</tr>
</thead>
<tbody>
<tr>
<td>With SU prophylaxis</td>
<td>47868</td>
<td>169</td>
</tr>
<tr>
<td>Without SU prophylaxis</td>
<td>25609</td>
<td>130</td>
</tr>
</tbody>
</table>

**Discussion**

The incidence of UGIB in patients undergoing cardiac surgery was found to be 0.45%. The incidence is low compared to general intensive care patients
Helicobacter pylori in the critically ill patient.

were 0.6 to 9% is found [3-7]. A few prospective endoscopic studies show that the incidence of ulcerations is greater but most of them will not bleed. Many of the aforementioned risk factors for the occurrence of UGIB are induced by a low cardiac output or induce a low cardiac output. Therefore, a low cardiac output or any intervention leading to a low cardiac output state will impair splanchnic blood flow and therefore increase the risk for gastro-intestinal complications. Christenson found a relative risk of 2.46 for the development of gastro-intestinal complications in patients with post-operative low cardiac output [22]. The use of inotropic support is related to a low cardiac output and is therefore significantly correlated with gastro-intestinal complications [38]. In addition, inotropes may reduce splanchnic output by their vasoconstrictive properties.

Specific pharmacological stress ulcer prophylaxis with histamine2-receptor antagonists or cytoprotective agents reduces back diffusion of acid in ischaemic intestinal mucosa, thus preventing further damage and ulcer formation. A recent study in general intensive care patients did not find sucralfate to be better than placebo and therefore ranitidine is the only drug found to be effective in preventing stress ulceration in critically ill patients [3]. Placebo controlled studies concerning pharmacological prophylaxis of stress ulceration in patients after CPB surgery have not been performed. We compared the incidence of UGIB in studies with and without pharmacological prophylaxis of stress ulcer in patients after cardiac surgery but did not find a significant difference. This result does not support the use of routine stress ulcer prophylaxis in patients undergoing cardiac surgery. The low incidence of UGIB makes it questionable whether stress ulcer prophylaxis can be cost-effective at all, even if significant reduction in stress ulcer formation would be reached. Furthermore, the use of histamine2-receptor antagonists may increase infection rate. In vitro leukocyte function appear to be enhanced by histamine receptor antagonists but these findings are in contrast with clinical findings [44]. The use of histamine receptor antagonists in critically ill trauma patients led to higher infection rates compared to patients without this medication [45]. Even single administration of histamine receptor antagonists pre-operatively resulted in a higher pneumonia incidence in patients after cardiac surgery [46]. Cimetidine has been shown to reduce splanchnic blood flow [47] and may lead to adrenal insufficiency [48]. The fact that controlled clinical trials concerning acid suppression for the prevention of stress ulceration in patients undergoing cardiac surgery have not been performed and the side effects that may occur using acid suppressive drugs should be reason not to use stress ulcer prophylaxis routinely.

An approach to prevention of stress ulceration and related bleeding in patients undergoing cardiac surgery and cardiopulmonary bypass can be
extracted from the considerations discussed above but no preventive strategy has been studied prospectively. Maximum effort should be exerted to preserve tissue oxygenation during surgery and in the intensive care unit. Hypovolaemia should be avoided and vasoconstrictive medication reduced. Vasodilators may be necessary to accelerate the relaxation of constrictive arterioles. Pulsatile flow during cardio-pulmonary bypass is preferred. Infection and hyperinflammatory state should be avoided. In a recent meta-analysis selective decontamination of the digestive tract (SDD) was found to reduce the incidence of ventilator associated pneumonia by 67% and mortality reduction was reduced by 20% in unselected critically ill patients [57]. When prolonged post-operative mechanical ventilation is expected in high risk patients pre-operative (SDD) may be used and should be instituted at least two days before the operation to reach adequate decontamination. Prevention of ventilator associated pneumonia and urinary tract infection prevents a hyperinflammatory state [23] which may lead to mucosal damage and stress ulcer formation. Other hygienic measurements should receive the highest attention for the same reason. Stress ulcer prophylaxis with histamine receptor antagonists should be restricted to high risk patients who are defined as prolonged mechanical ventilation or coagulopathy. Patients with a history of gastric or duodenal ulcers should also receive pharmacological prophylaxis but a possible exception may be made for patients who have had \textit{H. pylori} eradication.

\textbf{Conclusion}

Stress ulceration and associated bleeding has a complex and multifactorial pathophysiology. Haemodynamic, inflammatory and perhaps infectious factors play a role. The incidence in patients after cardiac surgery is low but in these patients mortality is relatively high. Prevention implies optimisation of haemodynamics. Prevention of infection and enhanced inflammatory state should receive appropriate attention. The routine use of stress ulcer prophylaxis by sucralfate of histamine receptor antagonists is not supported by appropriate studies.
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