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Agglutinins and cardiac surgery: a web based survey of cardiac anaesthetic practice; questions raised and possible solutions

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ABSTRACT

Introduction: Cardiac surgery involves cardiopulmonary bypass during which the core temperature is generally lowered to hypothermic levels. Patients presenting for cardiac surgery are sometimes reported to have cold or warm autoantibodies at the time of blood screening. It is known that cold agglutinins may cause potentially life-threatening haemolysis, intracoronary haemagglutination leading to inadequate cardioplegia distribution, thrombosis, embolism, ischaemia or infarction. The risk (if any) posed by warm autoantibodies is less clear. Because of the absence of hospital policies and of clear UK guidelines that explain how to manage such cases, we decided to conduct a web-based survey regarding standard anaesthesia practice in patients with both cold and warm autoantibodies presenting for cardiac surgery.

Methods: We devised a short electronic survey asking for responses to 8 questions on cold auto-antibodies and 2 on warm auto-antibodies. This was sent to all members of the Association of Cardiothoracic Anaesthetists. Responses were collated and expressed as percentages. Free text responses were analysed for trend or reported verbatim.

Results: The results of our survey demonstrate that there is no consensus on the appropriate management of such patients, with responses ranging from cancelling surgery to proceeding without additional precautions.

Conclusions: In collaboration with haematologists and taking into account the available evidence, our institution has now developed a management strategy for cardiac patients with cold autoantibodies. Further studies will be required to determine the usefulness of our algorithm in daily practice.

Keywords: *cardiac, surgery, cold, warm, auto-antibody.*

INTRODUCTION

Cardiac surgery involves the use of cardiopulmonary bypass (CPB) during which the core temperature is generally lowered to hypothermic levels. For this reason, the presence of cold agglutinins (CAs) is of particular significance for cardiac surgical patients. The main risk posed by CAs is of potentially life-threatening haemolysis. In addition, there is a risk of intracoronary haemagglutination leading to inadequate cardioplegia distribution, thrombosis, embolism, ischaemia or infarction (1-4).

In our institution (Royal Victoria Hospital, Belfast, UK) cold agglutinins are not routinely tested preoperatively. Despite this, the laboratory not infrequently reports the presence of either CAs or "non-specific cold autoantibodies" (NSCAs) on the pre-operative group and screen test. For the majority of patients, this is a novel finding and there are no pointers to clinical cold agglutinin

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disease, such as acrocyanosis or laboratory evidence of haemolytic anaemia. The cardiac anaesthesiologist is thus presented with a problem: are these CAs or NSCAs likely to be of clinical significance and, if so, what steps should be taken to minimise the potential risk?

In the absence of any hospital policy, the usual course of action in our institution has been to solicit haematological advice. Sometimes further tests are requested, delaying the proposed surgery, whilst on other occasions no specific action is prescribed. Adding to the general confusion, we have also encountered a small number of patients identified as having "warm" autoantibodies or agglutinins (WAs) at the time of preoperative screening for cardiac surgery. Because of the absence of any clear UK guidelines that explain how to manage such cases, we decided to conduct a web-based survey regarding standard anaesthesia practice in patients, presenting for cardiac surgery, with both cold and warm autoantibodies.

METHODS

We devised a short electronic survey consisting of 8 questions on CA/NSCAs and 2 questions on warm agglutinins in addition to one question about the identity of the responder's institute. This national survey was approved by the committee of the Association of Cardiothoracic Anaesthetists (ACTA) and the survey questionnaire was sent electronically to all ACTA members over a 1 month period in July 2011.

The 8 questions related to CA/NSCAs and the two relating to warm agglutinins are shown in *Table 1* below.

Responses were collated and the percentage positive response to each question calculated. Where free text was permitted in an answer, comments were analysed to identify trends or similarities. Where no trend existed, the response was reported verbatim. Since the questionnaire asked about the general experience of ACTA members, responses were assumed to reflect both adult and paediatric practice.

RESULTS

We received a total of 40 completed questionnaires from 19 separate cardiac surgical institutes, 18 from the UK and 1 from North America. 6 responders preferred not to reveal name of their institution. The distribution of responses in shown in *Table 2* below. These institutes carry either medium or high quantity work-load.

In response to question 1, most cardiac anaesthesiologists (87.5%) said they had heard of cold agglutination syndrome, however, 10% stated that they had not. One responder declined to answer.

In response to our second question, 37 out of 40 respondents (92.5%) had no protocol/guideline in their institute. However, 3 responders from different institutes did have an established policy in their place of work.

With regard to question 3, the majority of anaesthetists (60%) reported that they encountered less than 5 cases of non-specific cold autoantibodies per year in their practice. 27.5% said they never encountered this problem, 7.5% said they encountered between 5-10 cases per year and 2.5% stated that they experienced more than 10 cases each year in their practice.

For the next set of questions, options were provided and multiple answers were allowed. Responding to question 4: 85% of responders would refer a patient with cold autoantibodies to a haematologist and 45% said they would alter the conduct of cardiopulmonary bypass. 25% would also order further investigations. By contrast, a small number of responders (10%) stated that they would not take any action if a patient

Table 1 - *Questionnaire.*

Number	Question
1	Are you aware of cold agglutination syndrome Y/N
2	Are you aware of any protocol in your hospital for patients with non specific cold or warm blood antibodies for cardiac surgery Y/N
3	How often in your cardiac practice do you encounter patient with non specific cold antibodies: • > 10 times per year • 5-10 times per year • < 5 times per year • never
4	What action do you take (in patients with cold autoantibodies). Tick any that apply: • None • Order further investigations • Refer to haematologist • Alter the conduct of cardiopulmonary bypass • Other (please specify below)
5	If you order further investigations which of the following do they include. Tick any that apply: • CBC and differential • blood film • antibody titre • thermal amplitude • liver function test • coombs test • other (please specify below)
6	Preoperatively, how would you manage raised cold antibody titres. Tick any that apply: • No treatment • steroids • high dose IgG • plasmapheresis
7	If you alter the conduct of CPB which of the following would you consider. Tick any that apply: • Will not alter CPB conduct • Off pump surgery • Normothermia • Warm blood cardioplegia • Warm plus cold crystalloid cardioplegia • Fibrillatory cross clamp • Other Do you consider myocardial temperature monitoring Y/N
8	If the proposed surgery necessitated deep hypothermic circulatory arrest, would you (single answer): • Proceed with additional precautions • Proceed after informed consent (no additional precautions) • Cancel the surgery If you answered additional precautions please specify below
9	How often in your cardiac practice do you encounter patients with warm antibodies
10	What action do you take in patients with warm antibodies. Tick any that apply: • Refer to haematologist • Alter the conduct of CPB • Order further investigations • No action

Table 2 - *Distribution of responses from UK hospitals .*

Institution	No of respondents
Freeman Hospital, Newcastle upon Tyne, UK	4
Papworth, Papworth, UK	4
Guys and St Thomas, London, UK	3
Bristol Royal, Bristol, UK	3
Royal Victoria Hospital, Belfast, UK	2
Royal Infirmary of Edinburgh, Edinburgh, UK	2
John Radcliffe Hospital, Oxford, UK	2
The Royal Sussex County Hospital, Brighton, UK	2
Royal Brompton Hospital, UK	2
GJNH, Glasgow, UK	1
Aberdeen Royal, Aberdeen, UK	1
The General Infirmary, Leeds, UK	1
James Cook University Hospital, UK	1
Hammersmith Hospital, London, UK	1
Barts and London, London, UK	1
Southampton University Hospital, UK	1
Wythenshaw Hospital, UK	1
Northern General hospital, Sheffield, UK	1
Toronto General Hospital, Canada	1
Anonymous	6

were found to have cold autoantibodies preoperatively.

In response to question 5, when presented with a list of options, more anaesthesiologists appeared willing to request further investigations than the 25% who had stated that they would do so in answer to question 4. Antibody titre was the most popular choice (35%), followed by thermal amplitude, blood film and Coomb's test (each 27.5%). 12.5% responded that they would order further investigations following the haematologist's advice.

One respondent stated that thermal amplitude testing was not available in their unit.

In answer to question 6, the most popular choice was to refer the patient to a haematologist for preoperative management (37.5%), 27.5% would consider preoperative plasmapheresis, 20% would give preoperative steroids, 12.5% would consider high dose IgG and 7.5% said they would decide whether or not to provide preoperative treatment based on thermal amplitude results. A substantial number (30%) would not offer any treatment preoperatively. For the purposes of this question, we did not attempt to define "raised titres".

Next, we explored how the conduct of cardiopulmonary bypass should be altered in patients with high titre cold autoantibodies. The most popular option (70%) was to conduct the surgery at normothermia with 60% opting to also give warm blood cardioplegia. 47.5% also considered off-pump surgery (if feasible) and 20% would consider fibrillatory cross clamp as an option. Only 10% would include myocardial temperature monitoring in their perioperative strategy. 15% offered a free text answer that ranged from "would consult haematologist", "would perform literature review" to "would cancel the surgery".

Question 8 presented responders with a difficult scenario. This time the options offered were mutually exclusive and the answers ranged from 10% who would proceed to deep hypothermic circulatory arrest without any additional precautions to 27.5% who would cancel the surgery altogether. The most popular option was to go ahead with surgery but to take additional precautions (42.5%). 20% declined to answer the question. When asked to comment on the additional precautions to be taken, most respondents would seek further advice before proceeding. 15% would ask for hae-

matology advice whereas 17.5% preferred a multidisciplinary team approach. One respondent suggested conducting a literature review. Only 2 respondents appeared happy to devise a management plan without seeking further advice and both suggested using plasmapheresis preoperatively.

Questions related to warm autoantibodies. Question 9 revealed that this problem appeared to be less common with 45% saying they never encountered it and another 40% quoting an incidence of less than 5 times in a year in their practice.

We then asked on the action to be taken, five of those surveyed did not select any of the options. Of the offered options, the most popular was to talk to haematologists (chosen by 70%), 25% volunteered to alter the conduct of cardiopulmonary bypass and 12.5% would order further investigations. 17.5% would not alter any aspect of perioperative management.

DISCUSSION

This web-based survey demonstrates that there is considerable confusion with regard to the correct management of cardiac patients with cold or warm autoantibodies. In terms of cold autoantibodies, the survey shows that most cardiac anesthetists across the UK have the same experience as us. They see between 1 and 5 cases per year, they have no policy in place as to what to do with them, and the most popular and recurring option is to contact haematologists for advice and to do whatever they instruct. In terms of the actions taken, there is extreme variability with some anaesthetists willing to cancel surgery in any patient with CAs/NSCAs and others prepared to go ahead with deep hypothermia even in the face of high antibody titres. Clearly, both cannot be right. It is possible that some patients are being placed at risk whilst others are having life-saving surgery postponed unnecessarily.

With regard to warm autoantibodies, our survey showed that some cardiac anaesthesiologists never encountered the problem and that for some of those there was uncertainty about what to do next.

Warm autoantibodies, although responsible for the majority of autoimmune haemolytic anaemias (AIHAs), are active at normal body temperature meaning that cardiac surgery presents little in the way of additional risk for these patients. There is therefore no benefit in altering the conduct of cardiopulmonary bypass. Nevertheless, the finding of warm autoantibodies should not simply be ignored. Prompt referral to a haematologist for further investigation and management is the appropriate course of action as suggested by 70% of our respondents.

The remainder of this discussion will deal with cold autoantibodies since these present the greater potential risk for the cardiac surgical patient. Numerous case reports have discussed the investigation and management of cardiac patients with cold autoantibodies, however there is as yet no consensus on the best plan of action. There is an urgent need for institutional guidelines on the perioperative management of cardiac surgical patients with cold autoantibodies.

Cold autoantibodies in cardiac surgery. Typical CA's are IgM autoantibodies that react against I-antigens on the surface of erythrocytes. The cause of these CAs may be primary/idiopathic, or more commonly, secondary to an infective process (mycoplasma, infectious mononucleosis, other viral infections) or a lymphoproliferative disorder (5).

The broader term "cold autoantibodies" describes a spectrum of cold reactive proteins ranging from the non-specific type, to the typical IgM CA. The finding of a cold autoantibody on routine cross matching may

have a variety of implications depending on titre and thermal amplitude. Titre represents the highest dilution of the serum sample at which agglutination of red cells in the cold is still seen: the higher the titre, the greater the likelihood of clinically significant cold autoantibody activation. Low titre cold autoantibodies (<1:40) can be detected in virtually all normal subjects under appropriate conditions and are clinically insignificant. (6). Higher levels of autoantibody may predispose the patient to agglutination of blood in non-physiological situations (e.g. during induced hypothermia) whilst, most rarely, cold agglutinins can give rise to the cold agglutinin syndrome, a very rare type of autoimmune haemolytic anaemia (AIHA) with an estimated incidence of one case per million people per year (7). Amongst the cardiac surgical population the incidence of detectable cold autoantibody has been stated to be approximately 0.8% to 4% (8).

Thermal amplitude is the temperature below which antibody activation occurs. Most patients have no symptoms at normothermia, but those with high titre and high thermal amplitude CAs can suffer haemagglutination at lower temperatures. If CAs are active at temperatures which also permit complement fixation, haemolysis may result. In the context of CPB, the initiation of rewarming can lead to catastrophic haemolysis (5). Clues to the presence of intraoperative agglutination/haemolysis include visible agglutination in the cardioplegia circuit, intracoronary thrombosis, inadequate delivery of cardioplegia and high line pressures in the cardiopulmonary bypass circuit (2, 9). The consequence of this process can be devastating with myocardial or cerebral infarction and multi-organ failure.

Much of what is known about cold agglutinins and their consequences during cardiac surgery comes from case reports. Izzat et al. (4) report a case where agglutination of red blood cells occurred within a minute of initiation of antegrade cold blood cardioplegia at 10°C leading to embolization in the coronary microcirculation. When the agglutinates were noticed, a coronary sinus cannula was inserted through the right atrium and continuous retrograde cold crystalloid cardioplegia was infused. Agglutinates were noted to flush back from the coronary arteries into the aortic root and the patient did not show any signs of cardiac damage postoperatively. This suggests that agglutination *per se* may be remediable if prompt action is taken. Haemolysis on the other hand may be much less amenable to intervention. An interesting case report by Bracken et al (10) described cardiopulmonary bypass in a 67-year-old male patient with cold agglutinins that had gone undetected prior to surgery. During surgery, the red cells in the cardioplegia heat exchanger clumped and the patient was noted to have haemoglobinuria. On the evening of surgery, the patient developed a cold pulseless left leg and underwent a bedside revascularization procedure. He died on the second postoperative day of haemodynamic compromise. The authors commented that it is not clear that cold agglutinins were directly related to the terminal event.

In contrast to the numerous case reports, a recent study by Barbara et al. (11) examined the incidence and consequences of cold agglutinins in the cardiac surgical population over an 8-year period. They reported only one case of haemolysis among 16 patients with either cold agglutinin disease or detectable CAs between 2002 and 2010. No serious harm resulted. Their findings might lead one to conclude that the presence of CAs is of little clinical significance, however it is worth noting that very few of these patients were exposed to any degree of hypothermia. In only one case was the core temperature allowed to drift below 34°C and 14 out of 16 procedures deliber-

ately employed warm blood cardioplegia. The authors concluded that asymptomatic CAs can safely be managed at normothermia without the need for further testing. Nevertheless, some cardiac surgical procedures cannot be performed at normothermia, hence it is still important to be able to determine which cardiac surgical patients with CAs/NSCAs are at risk of agglutination/haemolysis during surgery.

Identification of patients at risk. The determination of risk is informed by both clinical history and laboratory tests.

Preoperative screening should include queries about symptoms/signs of cold agglutination including acrocyanosis, haemoglobinuria, jaundice, and pallor (12). Laboratory tests for haemolytic anaemia should also be used to determine whether or not the patient has the clinical syndrome of cold agglutination.

Given the non-physiological conditions during cardiac surgery, patients without preoperative symptoms or signs of haemolytic anaemia may still be at risk intraoperatively. In the absence of evidence of autoimmune haemolytic anaemia, the most useful laboratory tests on which to base an assessment of risk are thermal amplitude and plasma titre (13).

These are difficult tests to perform, as accuracy necessitates that the blood sample is maintained at 37°C until the serum has been removed. A titre of around 1:10 is typical in normal individuals and up to 1:40 may regarded as clinically insignificant. Haemolysis is rarely seen below titres of 1:1000 whilst individuals with the cold agglutinin syndrome typically have titres in excess of 1:10,000 (6). Antibody titre varies with temperature. The presence of high antibody titres at 4°C (1:10,000) and low antibody titres at 37°C (1:16) is typical. Yet, in some patients, antibody titres show a flatter thermal spectrum with a moderately high titre at 4°C (1:320) and a readily demonstrable titre at 37°C (1:64) (14). In the typical profile of CA reactivity, profoundly hypothermic temperatures cause intense red cell agglutination, a process that reverses on rewarming. By contrast complement fixation is a warm-reactive process. Hence, complement-mediated haemolysis will only occur if the spectrum of temperatures that provoke agglutination overlaps that required for complement fixation.

To summarise, the spectrum of risk posed by the presence of cold autoantibodies ranges from no risk at all to life-threatening red cell agglutination/haemolysis. In terms of cardiac surgery, the overall understanding is that patients with low-titre (<1:32), low-thermal amplitude CAs (<20°C) are not at particular risk of agglutination and may not warrant any alteration in surgical plan (8).

Management. Management of patients deemed to be at risk of agglutination/haemolysis consists of preoperative strategies to reduce antibody titre or reactivity and intraoperative alterations to the conduct of surgery.

Pre-operative strategies. Optimum pre-operative management for cardiac surgical patients with clinically significant CAs is still unclear. Administration of steroids, azathioprine and cyclophosphamide has not been shown to be of benefit (8).

There have been numerous reports of the use of plasma exchange in patients with CAs (2, 15-21). Plasma exchange is a complex procedure that must be performed at normothermia and has several attendant risks including that of infection and of creating large volume shifts, which may be badly tolerated by cardiac patients. Since most CA IgM is intravascular, up to 80% of it may be removed by single 5-litre plasma exchange (22). Despite this, reports of the effectiveness of plasma exchange in the management of patients with CA have been mixed, with some suggesting success (18) while others have shown no benefit (20).

IgG therapy is more costly but easier to administer than plasma exchange. A case report has shown that high-dose IgG administration just before cardiac surgery caused an 8-fold reduction in the titre of CAs. The mechanism of IgG's action remains unclear. The authors speculate that the high dose IgG provides a protective coating over the I-antigens on erythrocytes and in this way prevents agglutination (23).

Intraoperative alterations in the conduct of surgery. Several authors have reported successful outcomes from intraoperative measures taken to limit the haematologic and cardiac consequences of cold exposure in patients with CAs (24). The range of options for the intraoperative management of these patients is wide (1, 2, 4, 8, 9, 25-37). Reported strategies include:

- Warm blood cardioplegia: antegrade and/or retrograde
- Warm ischaemic arrest
- Warm crystalloid cardioplegia to flush coronaries followed by cold crystalloid cardioplegia

Irrespective of the technique employed, it is essential to limit systemic cooling during CPB so as to maintain the systemic perfusion temperature above the thermal threshold of agglutinin activity. It is important not to forget simple measures such as the use of warming mattresses, heating of anaesthetic gases intravenous fluids and blood products. Similarly, the operating room temperature should be elevated.

Management of intraoperative agglutination. Cold agglutinins may not be detected prior to surgery in some at risk patients (4, 9, 10, 26). First time detection of agglutination in the intraoperative period warrants immediate action to raise the core temperature to normothermia along with warm retrograde myocardial washout as described above. Further treatment should be directed towards ameliorating any resulting haemolysis or end-organ damage.

Further progress in our institution as a result of this national survey. The results of our survey were shared with colleagues in both transfusion medicine and general haematology. We were able to explain the particular risks posed by cardiac surgery whilst our haematological colleagues could give advice on how to establish the significance or non-significance of cold autoantibodies.

Working in collaboration with these experts, we developed local guidance (Royal Victoria Hospital, Belfast, UK) on managing cardiac surgical patients with preoperative cold autoantibodies (*Figure 1*). Briefly, the guidance recommends for all such patients to be investigated for symptoms/signs of haemolytic anaemia. In common with Barbara et al. (11), our guidance states that those patients with evidence of haemolytic anaemia must be referred to a haematologist for further management prior to surgery. Those patients without haemolytic anaemia may follow two pathways depending on the type of surgery. If the surgery is low-risk, it may be performed at modest hypothermia (34° C) with warm cardioplegia and without further testing. Surgery where significant hypothermia is necessary, or highly likely, requires thermal amplitude and titre testing preoperatively to determine the risk of agglutination/haemolysis. The early involvement of haematologists is essential in the perioperative management of this latter group of patients.

CONCLUSION

Cold or warm autoantibodies may be detected for the first time on the preoperative group and screen. Warm autoantibodies, although responsible for the majority of cases of autoimmune haemolytic anaemia, present little in the way of additional risk for cardiac surgical patients. Nevertheless, such patients should be referred to a haematolo-

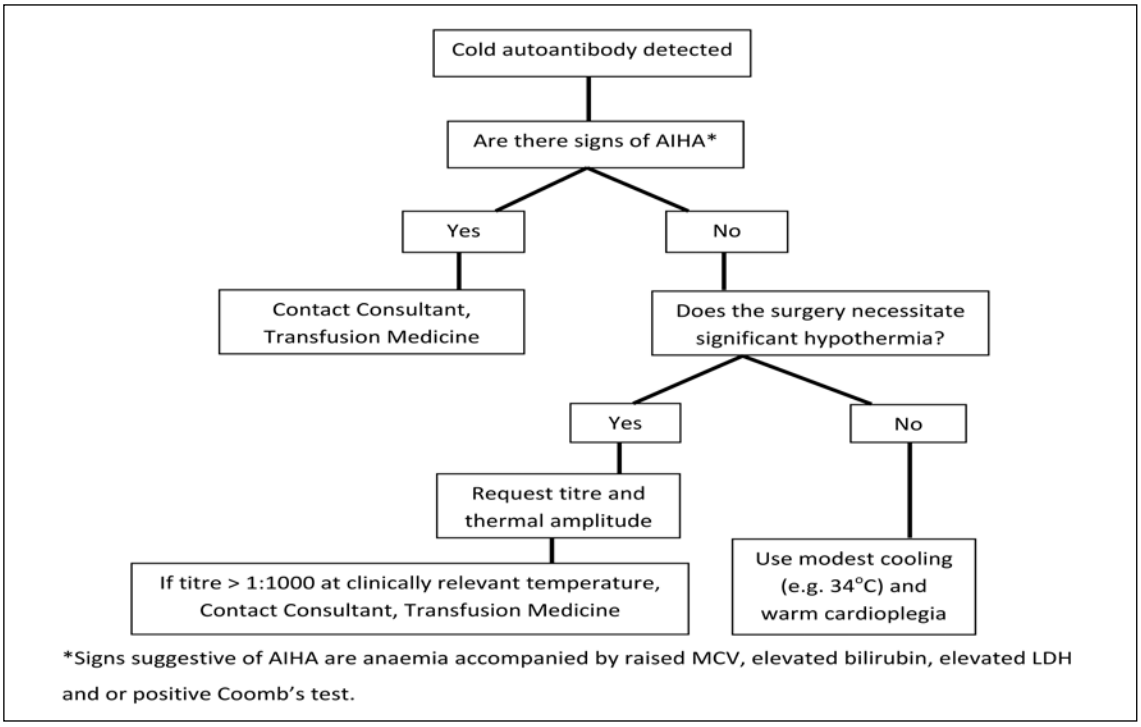

Figure 1 - *Algorithm for the management of cardiac surgical patients with cold autoantibodies. AIHA = autoimmune hemolytica; MCV = mean corpuscular volume; LDH = lactate dehydrogenase.*

gist for further investigation and management of their haemolytic anaemia. By contrast, cardiac surgery may pose additional risk for some patients with cold autoantibodies. Although many of these patients have a very low likelihood of agglutination/haemolysis if hypothermia is employed, the management of patients with high titre, high thermal amplitude cold autoantibodies require meticulous planning before cardiac operations.

The results of our survey demonstrate that the appropriate management of such patients remains unclear, with responses ranging from cancelling surgery to proceeding without additional precautions. Furthermore, the available literature yields no clear consensus on either the degree of risk posed by cooling or the antibody titre that precipitates a need for alteration in the conduct of surgery. Based on the results of this study, extensive literate review and collaboration with colleagues in haematology, we have developed and described a simple management algorithm for dealing with cardiac patients with cold autoantibodies. Further studies will be necessary to confirm the use of our algorithm in everyday practice.

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