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**Coronary artery bypass graft surgery in patients with recent exposure to
clopidogrel and aspirin therapy**

Enoch Akowuah, Vivek Shrivastava, and Graham Cooper

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22.5 ml of blood fills the left atrium from the pulmonary vein during systole. Because the systolic fraction of the pulmonary vein is 56% (of the systo-diastolic flow), we can assume that the total flow coming from the pulmonary vein (which reflects the total forward stroke volume) is 40 ml. Consequently, for the reported heart rate and body surface area, the cardiac index is 1.5 l/min/m², which is surprisingly low for a normal patient population. This rough calculation is enforced by the observation during transesophageal echocardiography that the diameter of the pulmonary vein does not change so much during the entire cardiac cycle. It has been shown that left atrial volume measured by echocardiography is underestimated compared with both cine-computed tomography (2) and magnetic resonance imaging (3). Would it not be useful to consider a physiologic variable such as cardiac output to evaluate the accuracy of volume measurement?

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REPLY

We appreciate the comments that Dr. Rossi expressed concerning our recent study (1) "Compensatory Changes in Atrial Volumes With Normal Aging: Is Atrial Enlargement Inevitable?" We are grateful to be given the chance to respond to the issues raised in the letter.

Our findings demonstrated that, in the younger age group, total left atrial volume change (passive emptying volume + conduit volume + active emptying volume) was approximately 60 ml per cardiac cycle. Thus, one may extrapolate that the left ventricular stroke volume in the absence of valvular regurgitation is approximately 60 ml. For a mean heart rate of 71 beats/min and body surface area (BSA) of 1.8 m², the cardiac output would be 4.3 l/min or 2.4 l/min/m², which is a reasonable estimate for the cardiac output of a normal young patient at rest. We agree with Dr. Rossi that correlating the left atrial volume estimation with cardiac output may be useful. However, we elected not to include the data, as insertion of a pulmonary artery catheter for measurement of cardiac output by thermodilution in our normal volunteers was difficult to justify. Estimating stroke volume by measuring the time velocity integral of the left ventricular outflow tract was not

included because the main thrust of the present study was on left atrial volume.

Furthermore, we believe that estimation of total left atrial volume change from pulmonary venous flow, which is suggested by Dr. Rossi, would ignore the all-important contribution of active atrial contraction to left ventricular filling, which would lead to an underestimation. However, we would like to emphasize that the potential for volume underestimation is always present with echocardiography. Thus, when estimating atrial volumes echocardiographically, the atrial volume should be maximized by selecting the largest frame, including the curve of the interatrial septum.

Moreover, we would also like to mention that the biplane atrial volumes obtained from transthoracic images do not account for atrial appendage blood volume. This exclusion of left atrial appendage volume may cause the underestimation in total atrial volume. Finally, when imaging at increased depths, the use of a lower frequency transducer may provide greater penetration, thereby optimizing atrial border visualization.

We sincerely hope that the above will adequately address the concern raised in Dr. Rossi's communication.

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Coronary Artery Bypass Graft Surgery in Patients With Recent Exposure to Clopidogrel and Aspirin Therapy

We read with great interest the study by Hongo et al. (1) entitled "The Effect of Clopidogrel in Combination With Aspirin When Given Before Coronary Artery Bypass Grafting." This very interesting study highlights an emerging problem for patients having routine coronary artery bypass graft surgery (CABG) after percutaneous intervention, as described in their report, but also for patients with an acute coronary syndrome who require urgent "in-house surgery" because these patients are invariably on both clopidogrel and aspirin therapy.

In their study, the investigators showed that continued clopidogrel therapy within seven days of elective CABG results in increased blood loss, increased use of blood products, and increased re-exploration rates. Unfortunately, although the study was pro-

spective there was no blinding of the nurses or clinicians to clopidogrel and aspirin exposure.

This lack of blinding is crucial to determine whether the main outcomes of the study are credible. The investigators acknowledged that recording of blood loss may be biased, but so could the decision to use blood and blood products (guidelines for the use of blood and blood products were not stated in their report). Also, no data were provided on the use of antifibrinolytic drugs. Use of drugs like aprotinin and tranexamic acid in patients with a high risk of bleeding is now well established, and this data would be relevant, particularly in patients who underwent re-exploration (2-4). Moreover, although the Society of Thoracic Surgeons' guidelines for re-exploration were used, these are open to interpretation, and the decision of a surgeon not blinded to clopidogrel therapy may be biased.

In addition, there was no measure of platelet function to demonstrate the fact that platelet aggregation was different between the two groups preoperatively and that this difference persists postoperatively and therefore directly accounts for the difference in postoperative bleeding and other outcome measures used. This is particularly important because the time from last clopidogrel dose to surgery ranged from 0 to 7 days, and in some patients, particularly those in whom clopidogrel therapy was stopped at least 5 days before surgery, other factors may have caused bleeding. In the Clopidogrel in Unstable Angina to prevent Recurrent Ischaemic Events (CURE) trial, patients in whom clopidogrel therapy was halted less than five days before surgery had a trend toward more major bleeding than those on placebo (9.6% vs. 6.3%, $p = 0.06$), whereas this trend was not seen in patients in whom surgery was performed more than five days after clopidogrel therapy was stopped (5).

In our experience, patients on clopidogrel and aspirin up to the time of surgery can be operated on safely provided a pro-coagulant drug like aprotinin or tranexamic acid is used intraoperatively. As discussed by Hongo et al. (1), antiplatelet therapy that is continued up to the time of surgery may be beneficial; in the case of aspirin it may improve mortality (6), and clopidogrel may reduce platelet activation owing to cardiopulmonary bypass (7,8). Until the question of the role of a pro-coagulant and platelet-protective drug (9) like aprotinin is defined, it is premature to conclude that surgery for patients with a history of clopidogrel exposure within seven days of operation should be delayed.

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REPLY

We are pleased that Dr. Akowuah and colleagues found our study (1) of interest. We acknowledge the inherent limitations of the study design, and we reiterate that further studies are needed to better define the role of clopidogrel before coronary artery bypass grafting (CABG) surgery. We believe it premature, however, to dismiss the credibility of the main outcomes of this study based on the lack of blinding. Chest tube output, the main measure of postoperative bleeding, is a highly objective and straightforward measurement. Because the nurses who recorded the amount of drainage were not aware of the questions being evaluated by the study, we have no reason to believe there was motive for misrepresentation. Reoperation for bleeding, the main clinical outcome, although a more subjective end point, was directed by institutional clinical guidelines. Patients went for reoperation when chest tube outputs either exceeded 300 ml over 2 consecutive h, or 500 ml over 1 h. As seen in Figure 1 of our study (1), patients with clopidogrel exposure who underwent reoperation all had 24-h chest tube outputs in excess of 4,000 ml, notably more than that of other patients.

The concern raised by Dr. Akowuah and colleagues regarding the use of antifibrinolytic agents is an important one. In our study, aprotinin was administered to eight patients (13.6%) exposed to clopidogrel and one patient (0.6%) without exposure. Any hemostatic effect of this agent would be expected to reduce adverse bleeding outcomes in the clopidogrel group, thus diminishing the differences seen between the groups. Ever since the completion of our study, we have started to use aprotinin routinely when immediate surgery is unavoidable in patients with clopidogrel exposure, and we are finding that perioperative bleeding is substantially reduced in most, but not all, cases. We echo the sentiment that the role of preoperative antiplatelet therapy in combination with antifibrinolytic agents is promising, but it is a role that is still undefined. Until further studies establish the efficacy of aggressive preoperative antiplatelet therapy, we maintain that caution should be exercised when patients ex-

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