Dopexamine increases internal mammary artery blood flow following coronary artery bypass grafting

Michael J. Flynn*, Desmond Winters, Patrick Breen, Gerry O’Sullivan, George Shorten, Damien O’Connell, Aonghus O’Donnell, Thomas Aherne

Departments of Cardiothoracic Surgery, Anaesthesia and Intensive Care Medicine, Cork University Hospital, Wilton, Cork, Ireland

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Abstract

Objective: Vasoactive agents and inotropes influence conduit-coronary blood flow following coronary artery bypass grafting (CABG). It was hypothesized that dopexamine hydrochloride, a dopamine A-1 (DA-1) and β2 agonist would increase conduit-coronary blood flow. A prospective randomized double blind clinical trial was carried out to test this hypothesis. DA-1 receptors have previously been localized to human left ventricle. Methods: Twenty-six American Society of Anaesthesiology class 2–3 elective coronary artery bypass graft patients who did not require inotropic support on separation from cardiopulmonary bypass (CPB) were studied. According to a randomized allocation patients received either dopexamine (1 μg/kg per min) or placebo (saline) by intravenous infusion for 15 min. Immediately prior to and at 5, 10 and 15 min of infusion, blood flow through the internal mammary and vein grafts (Transit time flow probes, Transonic Ltd.), heart rate, cardiac index, mean arterial pressure and pulmonary haemodynamics were noted. The data were analysed using multivariate analysis of variance. Results: Low-dose dopexamine (1 μg/kg per min) caused a significant increase in mammary graft blood flow compared to placebo at 15 min of infusion (P = 0.028, dopexamine group left internal mammary artery (LIMA) flow of 43.3 ± 14.2 ml/min, placebo group LIMA flow at 26.1 ± 16.3 ml/min). Dopexamine recipients demonstrated a non-significant trend to increased saphenous vein graft flow (P = 0.059). Increased heart rate was the only haemodynamic change induced by dopexamine (P = 0.004, dopexamine group at 85.2 ± 9.6 beats/min and placebo group at 71.1 ± 7.6 beats/min after 15 min of infusion). Conclusion: This study demonstrates that administration of dopexamine (1 μg/kg per min) was associated with a significant increase in internal mammary artery graft blood flow with mild increase in heart rate being the only haemodynamic change. Low-dose dopexamine may improve graft flow in the early post CABG period with minimal haemodynamic changes.

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1. Introduction

Previous authors have documented the effect of inotropes and vasoactive agents on conduit-coronary blood flow and particularly left internal mammary artery (LIMA) flow in coronary artery bypass grafting (CABG) [1–5]. This work was performed in animal models or in the free-flow situation. Dopamine subclass A-1 receptors have previously been identified in myocardial and renal tissue [6]. Dopexamine hydrochloride has been shown to cause in vitro vasodilatation [7] while in vivo studies have shown DA-1 receptor mediated vasodilatory effects in animal models [8,9] and clinically prior to distal anastomosis [10]. No clinical trial on the effect of dopexamine on coronary graft flow post anastomosis has been described.

The effects of some inotropes on coronary graft flow are mediated in part by vasomotor reactivity of conduit and coronary artery to specific receptor binding. Dopexamine hydrochloride is a moderately selective DA-1 and β2 adrenergic agonist. Based on the above it was hypothesized that administration of dopexamine hydrochloride (1 μg/kg per min) would increase conduit-coronary blood flow in the LIMA and saphenous vein grafts (SVG) post anastomosis. To test this hypothesis, a randomized controlled double blind trial was performed with patients randomized to receive either dopexamine or placebo (saline) post CABG.

* Corresponding author. Department of Cardiac Surgery, Freeman Hospital, High Heaton, Newcastle-on-Tyne NE7 7DN, UK. Tel.: +44-191-284-3313; fax: +44-191-222-6587.
E-mail address: barradrum@hotmail.com (M.J. Flynn).
2. Methods

With Institutional ethical approval and having obtained informed written consent, 26 elective CABG patients of American Society of Anaesthesiology (ASA) class 2–3 were studied. Only elective CABG patients in sinus rhythm were studied. Renal failure, diabetes mellitus and the need for inotropes on weaning from cardiopulmonary bypass (CPB) were exclusion criteria. Standard anaesthetic monitoring was performed (Datex). A central venous line and a pulmonary artery catheter with thermodilution continuous cardiac output monitoring (Vigilance, Baxter Inc., CA, USA) were inserted. A radial arterial catheter measured arterial pressure.

Anaesthesia was induced using fentanyl (100 µg/kg i.v.) and propofol (2–2.5 mg/kg i.v.) and muscle relaxation achieved using pancuronium (0.1 mg/kg). Propofol infusion (150–200 µg/kg per min i.v.) and isoflurane (0.5% inspired concentration) maintained anaesthesia.

Internal mammary artery harvesting was standardized to a non-skeletonized method, with distal division after heparinization and no topical vasoconstrictors were applied to the conduit. Each patient underwent a LIMA to left anterior descending coronary artery (LAD) pedicled graft and saphenous vein to right coronary artery grafting, using CPB with mild hypothermia (32 °C) and intermittent antegrade blood or crystalloid cardioplegia.

Topical cooling with ice slush was used as an adjunct to myocardial protection in all patients.

According to random allocation, patients received a 15-min intravenous infusion centrally of either dopexamine (1 µg/kg per min) or saline via a fully primed line after weaning from CPB, restoration of sinus rhythm and reversal of anticoagulation. The investigators were blinded to infusion identity until study completion. After heparin reversal, heart rate (HR), mean arterial pressure (MAP), cardiac index (CI), and pulmonary artery diastolic (PAD) pressure were measured. Pulmonary arterial wedge pressure was not measured as per the local ethics committee specifications in patients following recent systemic heparinization. LIMA to LAD flow and saphenous vein graft to right coronary artery were also measured. Flow measurements were performed by the senior authors (T.A. or A.O’D.) using transit time flow probes (Transonic HT107, 3 mm probe, Linton Instrumentation, Norfolk, UK) in ml/min. The use of transit time flow probes is described elsewhere [11].

Table 1. Age, gender, graft length and cardiopulmonary bypass duration

<table>
<thead>
<tr>
<th></th>
<th>Dopexamine group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (total)</td>
<td>8:6 (14)</td>
<td>7:5 (12)</td>
</tr>
<tr>
<td>Mean patient age (years) ± SD</td>
<td>67.5 ± 6.5</td>
<td>66.2 ± 6.2</td>
</tr>
<tr>
<td>Mean right coronary vein graft length (cm) ± SD</td>
<td>15.4 ± 2.3</td>
<td>14.3 ± 2.8</td>
</tr>
<tr>
<td>Mean LIMA length (cm) ± SD</td>
<td>13.3 ± 3.3</td>
<td>14.1 ± 3.0</td>
</tr>
<tr>
<td>Mean cardiopulmonary bypass time (min) ± SD</td>
<td>72.4 ± 11.4</td>
<td>68.6 ± 10.9</td>
</tr>
<tr>
<td>Blood cardioplegia</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Crystalloid cardioplegia</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

No vasoactive substances were used during weaning from cardiopulmonary bypass or during the study period. The need for any inotropic support, specifically adrenaline, dopamine, dobutamine, isoprenaline or phosphodiesterase inhibitors on weaning from cardiopulmonary bypass would have excluded patients from the study. Similarly, the requirement for an intra-aortic balloon pump (IABP) or vasoconstrictors (specifically noradrenaline) excluded the patient. Intravenous nitrates were not used on weaning from cardiopulmonary bypass and haemotocrit of 0.24 was achieved prior to weaning from CPB.

The first set of parameters was taken at time zero (commencement of infusion), and then at times 5, 10 and 15 min of infusion. Pre-infusion and post-infusion haematocrit, temperature and arterial pH, as well as graft length, were noted. These data were recorded using MacLab software (Apple Inc.).

Power analysis was used to determine the population size required. Calculations and transit time probe values for LIMA grafts are based on previously published data [11]. With a desired change, delta of 3.6 ml/min, with a beta value of 0.2, an alpha value of 0.05 and a standard effect size of 1.3, a requisite population size of 25 patients was calculated. Statistical analysis was performed using multivariate analysis of variance (MANOVA) (Minitab Inc., PA, USA) and P < 0.05 was considered as statistically significant. All results are presented with standard deviations.

3. Results

Fourteen patients received dopexamine and 12 received placebo (normal saline). The two groups were similar for the following criteria: age, gender, graft length, graft number and duration of CPB (Table 1). Pre-operative medication was also similar in both groups.

Heart rate, MAP, cardiac index and pulmonary arterial diastolic pressure were not significantly different between the two groups at baseline. The effect of dopexamine or placebo on the haemodynamics in both study groups is demonstrated in Table 2. The only significant change was an increased heart rate in the dopexamine recipients at 15 min of infusion (P = 0.004). All levels of significance quoted describe statistical significance relative to placebo.

Blood flow from LIMA to LAD and in the SVGs in both dopexamine and placebo groups were not significantly different at baseline (P = 0.13). During the period of dopexamine infusion, LIMA blood flow increased from 27.7 (3.4) ml/min to 43.3 (3.8) ml/min at 15 min (P = 0.028, Fig. 1). The increment in LIMA flow only.
became significant at 15 min of dopexamine infusion. Table 3 demonstrates LIMA flow at each time interval in the dopexamine and placebo group and statistical significance between the two groups. There was no significant change in the LIMA blood flow in the placebo group.

During the period of dopexamine infusion, saphenous vein graft flow increased from 41.9 (5.2) ml/min to 59.8 (6.7) ml/min. This did not achieve statistical significance over the effect of placebo on SVG flow (P = 0.059, see Fig. 2). In the placebo group, SVG flow increased from 32.3 (2.9) ml/min to 39.2 (4.8) ml/min, which did not achieve significance (P = 0.13) compared to baseline.

Table 4 demonstrates the saphenous vein graft (SVG) flow at each time interval in the dopexamine and placebo groups with statistical significance between the two groups.

Multivariate analyses using MANOVA demonstrated a statistically significant relationship between PAPD (pulmonary arterial diastolic pressure) and IMA flow at 15 min of dopexamine infusion (P = 0.016). There were no other significant relationships between changes in haemodynamic parameters and graft flow using multivariate analyses.

### 4. Discussion

The most important finding of this study is that intravenous infusion of dopexamine at 1 μg/kg per min in routine CABG patients following separation from cardiopulmonary bypass will safely increase LIMA-LAD blood flow with mild tachycardia (P = 0.004) being the only haemodynamic change. No significant alteration in SVG blood flow was noted.

In vitro study of human IMA has demonstrated the efficacy of dopexamine as a vasodilator [7]. The safety [12] and benefit of dopexamine in patients with normal and impaired left ventricular function is already proven [13]. The cardiovascular action of dopexamine is predominantly attributed to DA-1 and β2 adrenergic activity [14].

Other studies have documented the effects of inotropic agents on IMA flow. Agents investigated include enoximone, dobutamine, nitroglycerin, nitroprusside and epinephrine [1,8,10]. In the clinical setting, the only previously published studies of the effect of dopexamine on IMA flow have been on ‘free-flow’, i.e. after commencing CPB, with the IMA distally divided prior to cardioplegia and distal anastomosis completion [10]. However, this work demonstrated a statistically significant increase in IMA flow,
allowing for alteration in haemodynamics. Measurement of conduit blood flow prior to distal anastomosis is non-physiological and does not accurately reflect graft function post distal anastomosis [11,15], as no function of coronary vascular resistance is documented. The study we describe here was a double-blind clinical trial, with comparable study and control groups (age, gender, graft number, graft length, CPB duration, co-morbidity). Graft flow was measured post anastomotic completion after weaning from CPB without other inotropes or vasodilators.

Dopexamine at 1 $\mu$g/kg per min had no significant effect on SVG flow. Saphenous vein graft has been regarded as a passive conduit, but the absence of any change in SVG flow may represent absence of any effect on coronary artery ‘run-off’.

Heart rate was the only haemodynamic parameter that was significantly altered, with a mild tachycardia ($P = 0.004$). There were no alterations in the other parameters and notably cardiac index was not significantly increased. However, at dosages of greater than 1 $\mu$g/kg per min, others have shown that dopexamine significantly increased heart rate and dosages of 2–6 $\mu$g/kg per min significantly increased cardiac index [12]. Low-dose dopexamine caused a statistically significant tachycardia.

While the increase in heart rate from 71.1 to 85.2 beats/min may not be clinically detrimental, the clinical significance of this would be determined by measurement of myocardial oxygen consumption. Others have suggested that dopexamine increase oxygen consumption during cardiac surgery [16]. The current study does not assume that preservation of the hemodynamic parameters apart from heart rate, equated with no change in myocardial oxygen consumption.

Recent clinical trials of a highly specific DA-1 agonist, fenoldopam, have been published [17]. At dosages of 0.1 $\mu$g/kg per min no significant alteration in LIMA or SVG flow and minimal haemodynamic changes were documented, however, improved creatinine clearance was documented in the early post CPB period [18]. This suggests that the effect of dopexamine on LIMA flow may be mediated by $\beta_2$ receptor action.

Haematocrit is an important determinant of graft flow. While similar proportions of the study and control groups received blood and crystalloid cardioplegia, haematocrit was corrected to at least 0.24 prior to weaning from CPB.

It has been demonstrated the blood cardioplegia has superior endothelial reactivity preservation properties at microvascular level to crystalloid cardioplegia which may alter graft ‘run-off’ [19]. This, combined with the different effects of blood and crystalloid cardioplegia on haemodynamic performance on reperfusion, may alter graft flow. However, the distribution of blood and crystalloid cardioplegia patients within the dopexamine and placebo patients was similar in this study (Table 1).

Conduit-coronary blood flow can be altered by changes in cardiac index, mean arterial pressure, vasodilation of the conduit or alteration in ‘run-off’ in the coronary vasculature. Apart from graft blood flow, alteration of haemodynamics via positive inotropy or chronotropy may be detrimental on separation from CPB by increasing the oxygen debt of recently reperfused or stunned myocardium. Use of low-dose dopexamine may increase LIMA flow via $\beta_2$

![Error Bars show Mean +/- 1.0 SD](image)

**Table 3** The effect of dopexamine compared to placebo on IMA flow

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Placebo LIMA flow ± SD (ml/min)</th>
<th>Dopexamine LIMA flow ± SD (ml/min)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>24.1 ± 16.2</td>
<td>27.7 ± 11.6</td>
<td>0.63</td>
</tr>
<tr>
<td>5</td>
<td>24.4 ± 17.9</td>
<td>29.4 ± 13.4</td>
<td>0.79</td>
</tr>
<tr>
<td>10</td>
<td>26.3 ± 21.5</td>
<td>38.3 ± 15.9</td>
<td>0.415</td>
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<tr>
<td>15</td>
<td>26.1 ± 16.3</td>
<td>43.3 ± 14.2</td>
<td>0.028</td>
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</tbody>
</table>

**Fig. 2.** The effect of dopexamine and placebo on SVG flow.
adrenergic action, with minimal haemodynamic alteration in the early post-operative period, and may have clinical implications in patients with impaired left ventricular function undergoing CABG.

4.1. Study limitations

Distal coronary artery ‘run-off’ is a vital component of graft flow. The study of coronary artery bypass function within a group of only 26 patients with different coronary disease patterns is a major limiting factor. To accurately study the effect of dopexamine on saphenous vein grafts and left internal mammary arteries, it would be necessary to anastomose either SVG or LIMA to coronary systems of equal ‘run-off’. The left anterior descending and right coronary systems are rarely comparable in this regard. Increasing the patient number would lessen this limitation. Secondly, the senior authors in this study used different cardioplegic methods (i.e. blood or crystalloid). Crystalloid cardioplegia may alter IMA endothelial function and thereby alter vasoactivity of the conduits.

References


<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Placebo LIMA flow ± SD (ml/min)</th>
<th>Dopexamine LIMA flow ± SD (ml/min)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>32.3 ± 9.5</td>
<td>41.9 ± 20.7</td>
<td>0.112</td>
</tr>
<tr>
<td>5</td>
<td>37.9 ± 19.2</td>
<td>49.4 ± 23.7</td>
<td>0.151</td>
</tr>
<tr>
<td>10</td>
<td>40.8 ± 26.4</td>
<td>57.2 ± 24.9</td>
<td>0.295</td>
</tr>
<tr>
<td>15</td>
<td>39.2 ± 16.5</td>
<td>59.8 ± 25.1</td>
<td>0.059</td>
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