The Relationship Between Diastolic Pressure and Coronary Collateral Circulation in Patients With Stable Angina Pectoris and Chronic Total Occlusion

Wang Shu,1 Jing jing,1 Liu Chang Fu,1 Jiang Tie Min,2 Yang Xiao Bo,1 Zhou Ying,1 and Chen Yun Dai1,*

BACKGROUND
The most important biomechanical source of activation of the coronary collateral circulation (CCC) is increased tangential fluid shear stress at the arterial endothelial surface. The coronary circulation is unique in that most coronary blood flow occurs in diastole. Consequently, the diastolic blood pressure (DBP) may influence the tangential fluid shear stress on the arterial endothelial surface in diastole, thereby affecting development of the CCC.

METHODS
To investigate this, we conducted a study of 222 patients with stable angina pectoris and chronic total occlusion of coronary arteries. All of the patients had no history of coronary artery interventional therapy, coronary artery bypass surgery, cardiomyopathy, or congenital heart disease. The extent of the collateral vasculature of the area perfused by the artery affected by chronic total occlusion was graded as poor or well-developed according to Rentrop's classification.

RESULTS
Univariate analysis showed a significant difference between the study subgroup with poorly developed collaterals and that with well-developed collaterals in terms of high diastolic blood pressure (DBP) and mean DBP. Multivariate analysis revealed high DBP as the only independent positive predictor of a well-developed collateral circulation.

CONCLUSIONS
High DBP is positively related to a well-developed CCC. Differences in development of the CCC may be one of the pathophysiologic mechanisms responsible for the J-curve phenomenon in the relationship between DBP and cardiovascular risk.

Keywords: coronary collateral circulation; diastolic blood pressure; tangential fluid shear stress; J-curve phenomenon; blood pressure; hypertension.

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Coronary collateral circulation (CCC) has long been acknowledged as a natural bypass for blood supplying myocardium jeopardized by ischemia. More than 200 years ago, Heberden described a patient who had been nearly cured of his angina pectoris by sawing wood each day. This phenomenon was traditionally ascribed to coronary vasodilation, with the opening of collateral vessels to support the ischemic myocardium.1 In 1989, Hsusen demonstrated that well-grown collateral arteries could protect the myocardium by preventing acute myocardial infarction and heart failure, thus improving survival.2 Since then, several studies have proven that the condition of the CCC determines the survival of the myocardium upon total occlusion of the arteries that normally supply it with blood.3-8 Recently, a meta-analysis by Meier et al.7 showed that patients with a high degree of collateralization have a 36% lower risk of mortality than those with a low degree of collateralization. Because of the great importance of the CCC, considerable research has focused on the factors that promote it. Clinical factors consistently described as determining the extent of collateralization in the human heart are the severity of coronary artery stenoses9-10 and the duration of symptoms of myocardial ischemia.10,11 Inconsistently described factors favoring the development of coronary collateral vessels are young age,12 male gender,13 a low heart rate,14 and hypocholesterolemia.15 Information about the influence on collateral development of other clinical factors, such as diabetes mellitus, is discordant.13,14,16 The presence of systemic hypertension has also been suggested as promoting a well-developed CCC. Kyriakides et al.18 indicated that patients with systemic hypertension and coronary artery disease have an increase in their CCC.

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ORIGNAL ARTICLE

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trigger of arteriogenesis is increased tangential fluid shear stress at the endothelial surface.\textsuperscript{19} Tangential fluid shear stress is closely related to fluid flow velocity, and in vivo, blood (fluid)-flow velocity will affect tangential fluid shear stress. In turn, blood pressure (BP) determines blood flow velocity in vivo. The coronary circulation is unique among vascular beds in that most coronary blood flow to the myocardium occurs in diastole.

Consequently, we hypothesized that diastolic blood pressure (DBP) might influence tangential fluid shear stress on the endothelial surface by influencing coronary artery blood-flow velocity in diastole, thereby affecting the development of the CCC.

To investigate this, we conducted a study to examine the predictors of a well-developed collateral circulation in patients with stable angina pectoris (SAP) and chronic total occlusion (CTO) of a major coronary artery, and to evaluate on a preliminary basis the effect of DBP on the development of a CCC.

\section*{METHODS}

\section*{Patients and clinical parameters}

During the 5-year period from June 2007 to June 2012, 222 patients (with a mean (±SD) age of 60 ± 11 years) who had both SAP and CTO, of whom 200 were men, were selected in the study. Total occlusion was defined as an interruption of vessel continuity, as assessed through angiographic imaging of a major coronary artery, without any antegrade flow. The duration of coronary artery occlusion was estimated from the date of occurrence of myocardial infarction (MI) in the area of myocardium supplied by the occluded vessel, from an abrupt worsening of existing angina pectoris, or from information obtained from a previous angiogram. Chronic total occlusion was defined as total occlusion of an estimated duration of more than 3 months.\textsuperscript{20} Patients were excluded from the study if they had a history of coronary artery interventional therapy, coronary artery bypass surgery, cardiomyopathy, or congenital heart disease.

The variables tested included age, gender, body mass index (BMI), left-ventricular ejection fraction (LVEF, evaluated through two-dimensional echocardiography), duration of coronary artery occlusion, diabetes mellitus, hypertensive disease, a high DBP, use of antihypertensive medication, smoking, a history of MI, systolic blood pressure (SBP), DBP, pulse pressure (PP), mean arterial pressure (MAP), serum lipids (cholesterol, high-density-lipoprotein (HDL)-cholesterol, low-density-lipoprotein (LDL)-cholesterol, triglycerides), fasting blood glucose (FBG), creatinine (Cr), and hematocrit (Hct) (Table 1).

Patients were defined as having a high DBP if they were both diagnosed as having hypertensive disease and had a DBP \(\geq 90\) mmHg. The DBP was measured on the morning after the patient had been admitted to the hospital. The patient did not take a morning dose of antihypertensive medication, if this was ordinarily needed, before the measurement. Blood pressure was measured with a standard mercury sphygmomanometer with an appropriately sized cuff applied to the upper nondominant arm at heart level.

Systolic blood pressure in the brachial artery was recorded at the first Korotkoff sound by auscultation, and DBP was recorded at the disappearance of the last Korotkoff sound. Blood pressure was measured thrice, at intervals of least 2 minutes, and the measurements were averaged.

\section*{Coronary angiography and assessment of collateral circulation}

Two specialists, who did not know the clinical conditions of the patients, read the coronary arteriographic data for each patient to assess the patients coronary artery lesion and CCC. The nonoccluded artery was first visualized for accurate evaluation of the extent of the collateral circulation to the area perfused by the chronically and totally occluded artery. The collateral circulation was graded with the Rentrop classification according to the extent of epicardial coronary artery filling through collateral channels injected with a contrast agent administered from the contralateral side, with grade 0 = no opacification; grade 1 = filling of side branches of the artery perfused through collateral vessels without visualization of the epicardial segment; grade 2 = partial filling of the epicardial segment through collateral vessels; and grade 3 = complete filling of the epicardial segment through collateral vessels.\textsuperscript{9} The patients were classified into two groups according to the degree of angiographic collateral flow, with one group having poorly developed collaterals (collateral indices of 0 or 1) and the other having well-developed collaterals (collateral indices of 2 or 3).

Definition of the number of coronary vessels diseased included stenosis of \(\geq 70\%\) of the left anterior descending (LAD), left circumflex (LCX), or right coronary artery (RCA) or their main branches or both. When a lesion involved only one coronary artery it was defined as single-vessel disease, as double-vessel disease when it involved two arteries, and as three-vessel disease when it involved three arteries. When the degree of stenosis of the left main coronary artery (LM) was \(\geq 50\%\), a lesion was defined as being combined with LM disease.

\section*{Statistical analysis}

Statistical analysis was done with the SPSS software package (SPSS, Chicago, IL). Univariate analysis of all categorical and continuous variables, with regard to the two study groups (well-developed and poorly developed collateral groups, respectively) was done with the chi-square test and unpaired Student’s t-test. Multivariate analysis (backward stepwise multiple logistic regression) was done on all clinical and angiographic factors to identify significant predictors of the presence of a well-developed collateral circulation. Statistically significant differences were defined as those with a value of \(P < 0.05\).

\section*{RESULTS}

\section*{Univariate analysis of clinical data}

Univariate analysis showed no statistically significant difference between the study subgroups with a poorly developed collateral circulation and a well-developed collateral circulation in terms of gender, age, BMI, or LVEF (Table 1).
Furthermore, there was no significant difference in the cardiovascular risk profiles of the two subgroups, such as the presence of diabetes mellitus, hypertensive disease, smoking, hypercholesterolemia, duration of coronary artery occlusion, or history of MI (Table 1). There was a significant difference between the subgroups in terms of the prevalence of high DBP and in mean DBP (Table 1). Beyond this, there was a positive correlation between high DBP and a well-developed CCC (Figure 1). There was no difference in the two subgroups in terms of SBP, PP, MAP, use of antihypertensive medication, serum FBG, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, Cr, or Hct (Table 1).

Univariate analysis also showed no statistically significant difference between patients with poorly developed collaterals and those well-developed collaterals in terms of the position of the lesion causing CTO (Table 2). Nor was there a statistically significant difference between the subgroups in the number of coronary vessels diseased or in the condition combined with LM disease (Table 2).

In multiple regression analysis with clinical and angiographic variables, high DBP was the only independent positive predictor of a well-developed collateral circulation ($P < 0.01$).

**DISCUSSION**

The analysis in the present study, involving 222 patients with SAP and CTO, revealed that a well-developed CCC, as assessed with the Rentrop classification, was influenced only by high DBP.
Fluid shear stress

Fluid shear stress, which activates mechanotransducers on the endothelial cell membrane, is a hemodynamic stimulus for arteriogenesis and the development of a CCC. It has been proposed that stretch-sensitive potassium channels and transiently phosphorylated focal adhesions on the cell membrane act as mechanotransducers for this process. Furthermore, shear stress could moderate the expression of endothelial nitric oxide synthetase, whose product, nitric oxide, permeabilizes endothelium. It is yet unresolved how the mechanical force on these transducers is translated from the endothelial-cell membrane to the nucleus.

Patient selection

The degree of coronary artery stenoses is consistently described as positively determining the extent of coronary vascular collateralization in humans. We chose patients with CTO for this study so that all would have the same degree (100%) of coronary artery stenoses. Consequently, the impact factor (the degree of coronary artery stenoses) on CCC was not a factor in the results of the study. We chose patients with SAP because they have a high rate of having a well-developed CCC. In our study, the percentage of patients with a well-developed CCC was about 83%. These factors increase the likelihood of identifying the factors that influence the development of a CCC in patients with CTO and SAP.

High diastolic blood pressure as a factor in the development of a collateral circulation in humans

Previous studies of the effect of BP on the development of a CCC have focused on the history of hypertension or MAP. However, DBP plays a more important role in myocardial blood supply. Because the coronary arteries are perfused predominantly during diastole, the J-curve phenomenon, in which the diastolic pressure is inversely related to the risk of coronary heart disease and adverse outcomes, has been observed in numerous studies. Three pathophysiological mechanisms have been proposed to explain the existence of the J-curve phenomenon: (i) a low DBP could be an epiphenomenon to coexisting or underlying poor health or chronic illness, leading to increasing morbidity and mortality (reverse causality); (ii) a low DBP could be caused by an increased PP reflecting advanced vascular disease and stiffened large arteries; and (iii) overly aggressive antihypertensive therapy could lead to an excessively low DBP and thus to hypoperfusion of the coronary vasculature, resulting in coronary events.

Table 2. Results of univariate analysis of coronary angiographic data

<table>
<thead>
<tr>
<th></th>
<th>Poorly developed collaterals</th>
<th>Well developed collaterals</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 38)</td>
<td>(n = 184)</td>
<td></td>
</tr>
<tr>
<td>Position of chronic total occlusion lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>14 (36.8%)</td>
<td>80 (43.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>LCX</td>
<td>6 (15.8%)</td>
<td>42 (22.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>RCA</td>
<td>18 (47.4%)</td>
<td>62 (33.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Combined with LM disease</td>
<td>6 (15.8%)</td>
<td>26 (14.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Number of coronary vessels diseased</td>
<td>2.4 ± 0.7</td>
<td>2.2 ± 0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as the number (%) of patients or mean value ± SD.

Abbreviations: LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; RCA, right coronary artery.
However, it is not known why hypoperfusion of the coronary vessels may result in coronary events. In the present study we demonstrated a positive correlation between high DBP and a well-developed CCC (Figure 1). Because of the protective effect of CCC in patients with CAD, we speculate that DBP may influence the prognosis of patients with CAD through its influence on the development of a CCC. On the other hand, the reduction of DBP may reduce the tangential fluid shear stress at the endothelial surfaces of coronary arteries. This biomechanical change could result in a poorly developed CCC. The effect of DBP on CCC may be a new pathophysiologic mechanism by which to explain the J-curve phenomenon.

In this study, we took a DBP of 90 mm Hg as the demarcation level for determination of a high DBP. Previous studies have used different levels of the J-point of DBP, with the lowest being a DBP of 60–65 mm Hg and the highest a DBP of 100–109 mm Hg. Ma et al. showed that in women with type 2 diabetes, the optimal range of DBP is 67–77 mm Hg, within which the risk of CHD is lowest. Vamos et al. found that low BP, particularly below 110/75 mm Hg, is associated with an increased risk of all-cause mortality in people with newly diagnosed type 2 diabetes. Recently, Vishram et al. indicated that a DBP < 71 mm Hg had a significant inverse relation to the risk of stroke.

In clinical practice, patients with a DBP > 90 mm Hg are usually advised to take antihypertensive drugs. Consequently, we selected 90 mm Hg as the lower cutoff level for DBP in our study. In this study, 92% of the patients in the high-DBP group, and 86% of those with a DBP < 90 mm Hg, had taken at least one antihypertensive drug. Cardioprotective effects of some antihypertensive drugs (e.g., beta-blockers) may be a reason for the high utilization of antihypertensive drugs in these patients.

Our study has some limitations. First, we used angiography to assess CCC qualitatively. Angiography is the "gold standard" for confirming the anatomic structure of the coronary artery and CCC. The collateral flow index (CFI) is a quantitative method of assessing the function of CCC, and combining angiography with the CFI could be a more accurate way of determining the extent of CCC. However, only angiographic data were available for the present, retrospective study. We are planning a prospective study in which we will judge CCC by both angiography and CFI. We propose to divide DBP into several levels to determine the exact J-point between DBP and CCC.

Because estimates of the duration of coronary artery occlusion in the present study were based on information obtained from a previous angiogram or on a patient's symptoms or the results of physical examination, estimation of the time of CTO may not have been exact.

The LCA has a predominantly diastolic blood flow whereas the RCA receives both systolic and diastolic flow. Recently, Khoueiry et al. proved that aortic PP may affect CAD as well as the phasic patterns of coronary blood flow. In this study we did not determine whether there was a distinction between DBP and CCC if the CCC was fed by the LCA as opposed to the RCA.

The present clinical study of patients with SAP and CTO, with the assessment of their CCC according to the Rentrop classification through coronary angiography, reveals that a high DBP is positively related to a well-developed CCC. The differential development of a CCC may be one of the pathophysiologic mechanisms for the J-curve phenomenon relating DBP to cardiovascular risk.

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**DISCLOSURES**

The authors declared no conflict of interest.

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