A Novel Hypothetical Method to Increase the Dimensions of the Coronary Arteries when Required

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Abstract

Background
The purpose was to develop a novel hypothetical method to increase the size of coronary arteries.

Methods
During long-term observation an increase in coronary size has been seen in three unexpected scenarios. Changes in coronary artery sizes were observed in patients with mitral stenosis (n=69) by angiogram prior to percutaneous balloon mitral valvuloplasty or valve replacement surgery for severe mitral stenosis. The coronaries of patients with patent ductus arteriosus who underwent surgical closure in the past (n=14) were examined by echocardiogram. Patients with renal failure on long-term dialysis through peripheral arterio-venous fistula without left ventricular hypertrophy (n=17) were studied by echocardiography. Normal age, weight and sex matched coronary sizes served as controls in the study. All these observations were made over a period of 12 years.

Results
The sizes of coronaries in patients with mitral stenosis, patients who underwent closure for patent ductus arteriosus, and in patients on hemodialysis through arteriovenous fistulas were higher than normal controls (p<0.05, for all). A hypothetical model to increase the coronary sizes could be developed based on the analysis of the differential equations of Poiseuille's. A method is proposed of creating a peripheral arterio-venous fistula, which could be closed later electively by a percutaneous method/surgery. The closure time needs to be determined by experimental studies. The other methods could be a continuous exercise program or by the use of beta-blockers.

Conclusions
A novel hypothetical method of peripheral arteriovenous fistula formation is described which could potentially increase the size of the coronaries, which could be closed later.

Keywords: Coronary dimensions; Poiseuille’s Equation; Arteriovenous fistula; Coronary dilatation; Wall shear stress; Coronary blood flow; Atherosclerosis; Angiogenesis

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scenarios a theoretical model has been proposed as a derivative of physical equations governing fluid dynamics.

**Methods and Results**

The study was developed after the observation of a series of cases in different clinical settings in which the coronary arteries appeared dilated. Three clinical conditions were identified and studied, in which the coronary arteries were widened, and the left ventricles had normal dimensions. In these three clinical conditions an increase in coronary sizes was not expected. Conditions which are known to increase or decrease the coronary and left ventricular dimensions were excluded. After observations in the initial three years, a prospective case-controlled study was planned. The primary outcome of the study was to identify dilated coronaries in patients with normal left ventricular dimensions, compared to the controls. The recruitment of the patients was on a continuous non-randomized method. This is due to a limited number of patients available for the study. The study was not blinded, and the author was aware of the subjects as well as the controls. The observations were made over a period of 12 years. Coronary diameters were measured in the left main coronary artery (LMCA), left anterior descending artery and the right coronary artery within 3mm from the coronary ostium (Philips IE33, HP Sonos 5500 and Sonosite M-Turbo).

**Rheumatic Mitral Stenosis**

Observations in the coronary angiograms (n=32) (Siemens Axiom Artis) before mitral balloon valvuloplasty (figure 1) or as a preoperative workup (n=13) for a mitral valve replacement for severe calcific mitral stenosis (figure 2) showed a mild increase in the coronary sizes instead of the expected small caliber since the left ventricle is usually small in this condition compared to the controls (figure 3). During this period balloon mitral valvuloplasty was performed in 157 patients. However, a coronary angiogram was performed in only 32 patients. The mean age of the patients was 38±9 yrs. (median 37, range 18 to 57 years).

In a further subset of 24 patients out of the 157 patients who underwent balloon mitral valvuloplasty, left ventricular angiograms were performed in the initial period before the year 2011 (Figure 4). The patient profile was similar to those patients who underwent balloon mitral valvuloplasty subsequently after year 2010. In these patients, direct coronary angiogram was not performed, and it was a protocol to perform left ventricular (LV) angiogram at that time to look for the mitral valve calcification and to quantify the extent of mitral regurgitation. Diagnostic coronary angiogram as a routine was performed only in patients more than fort-five years, which is a standard guideline. These patients LV angiograms were reviewed and the mean LMCA 4.3±0.3mm and LAD 3.5±0.2mm dimensions were significantly higher than the normal controls. Also, none of these patients had coronary artery disease.

The mean age of patients who underwent surgery (mitral valve replacement) for isolated severe mitral stenosis was 43±6 yrs. (n=13). (median 45; range 28 to 58). Patients with other valvular lesions and mitral regurgitation were excluded. All these patients underwent coronary angiography before the surgical procedure (supplementary figures 6 and 7). All the patients successfully recovered after surgery. Patients with any hyperdynamic circulatory states such as anemia, pregnancy or thyrotoxicosis, and patients with hypertension or the presence of left ventricular hypertrophy were excluded.

![Figure 1](image1.png)

*Figure 1*

Shows the coronaries of a patient with rheumatic mitral stenosis (panels A, B, C and E) prior to balloon mitral valvuloplasty (panel D), magnification factor 17.

![Figure 2](image2.png)

*Figure 2*

Angiogram in a patient with severe mitral stenosis prior to mitral valve replacement (magnification factor 17).
Creatinine levels were normal except in 1 patient where the creatinine was 1.4 mg/dl, and the coronaries were not dilated in this patient. The mean left main coronary artery (LMCA) diameter 4.2±0.2mm was, and the mean proximal right coronary artery (RCA) 3.2±0.3mm diameter and proximal LAD 3.4±0.2mm diameters and the proximal left circumflex artery (LCA) were 3.3±0.3 mm. None of these patients had coronary artery disease (figures 1 and 2, and supplementary figures 1 to 7).

The control patients (n=32) were patients with normal chamber dimensions and normal coronaries who underwent coronary angiography for evaluation of chest pain after a stress test. The control patients were age-sex-weight matched without other co-morbidities or valvular disorders, and they were selected retrospectively in a randomized non-blinded fashion. The control (figure 3 and supplementary figures 8 to 12) values of the normal coronary artery sizes in a similar age and body size-matched controls for LMCA was 3.4±0.3mm, proximal LAD was 2.9±0.3mm, the proximal RCA was 2.7±0.3mm, and the proximal LCA - 2.8±0.2mm. The values were significant by t-test (p<0.05, for each). Baseline characteristics are given in the table 1. Out of the total 69 patients in this category, 57 had dilated coronaries compared to control, six had only mildly dilated vessels, five had normal sized vessels; one patient had a smaller vessel and this patient had higher creatinine value of 1.4mg/dl.

Patent Ductus Arteriosus

Patent ductus arteriosus is a congenital vascular connection between the aorta and pulmonary artery. Patients (n= 14) with large shunts who underwent surgery in the past were analyzed for the coronary sizes by echocardiography. Baseline characteristics of this patient group is given in table 2. It was observed that the coronary arterial sizes were larger than the usual, which was observed by echocardiography analysis. The size of the aorta in these patients was normal. In all these cases surgical/coil closure was performed at least four years before the echocardiography these observations of coronary dilatations (figure 5, upper panel, Figure 6A and 6B). The mean age of the patients was 17±7 yrs. None of the patients had hyperdynamic circulations such as with
anemia, thyrotoxicosis or peripheral arteriovenous fistula. The mean LMCA diameter was 4.28±0.4mm, LAD was 3.6±0.3, and the mean RCA diameter was 3.4±0.2mm.

The control patients (n=13) were normal age-sex-weight matched patients without other co-morbidities. They had normal chambers and coronary dimensions and there were selected by a randomized method. The control values of normal LMCA, LAD and RCA measured by the similar technique was 3.4±0.4mm, 3.0±0.3mm and 2.8±0.3mm respectively. The values were statistically significantly different (p<0.05, for each). The RCA was co-dominant or dominant in all these cases. Visual assessment (eyeballing) of the coronary arteries showed a significant increase in the size of the coronary vessels in these patients compared to the similar age and body-size matched controls (figure 7). All echocardiographic measurements of the coronary arteries were performed with the same magnifications. Also, in all the cases except one, the coronary arteries were dilated compared to the controls giving a high statistical power.

Table 1. Baseline characteristics of patients undergoing balloon mitral valvuloplasty/surgery.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values, n=69(32BMV&gt;2010+24BMV&lt;2011+13Surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs.</td>
<td>37±9</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>22/47</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>1</td>
</tr>
<tr>
<td>MV area Pre-procedure, cm²</td>
<td>0.9 ± .1</td>
</tr>
<tr>
<td>MV area Post procedure, cm²</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166 ±5</td>
</tr>
<tr>
<td>Left ventricle size, mm</td>
<td>46 ± 0.2</td>
</tr>
<tr>
<td>Balloon size used, size mm, (n=52)</td>
<td>24, (62); 26(7)</td>
</tr>
<tr>
<td>Preprocedural mitral regurgitation (Gr 1), n</td>
<td>8</td>
</tr>
<tr>
<td>Preprocedural Pulmonary artery systolic pressure, mm Hg</td>
<td>82±10</td>
</tr>
<tr>
<td>Serum Creatinine, mg/dl</td>
<td>0.9±0.2</td>
</tr>
<tr>
<td>Atrial fibrillation, n</td>
<td>41</td>
</tr>
<tr>
<td>Periprocedural mortality, n</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Patients on hemodialysis through the peripheral arterio-venous (AV) fistula

Patients who undergo dialysis (n=17) with peripheral arteriovenous fistula were analyzed for their coronary sizes. Patients who already have left ventricular hypertrophy/dilatation were excluded, as a left ventricular hypertrophy/dilatation could increase the size of the coronary vessels to overcome the demand-supply mismatch in coronary blood flow. The control patients (n=17) were normal healthy age, sex and weight matched controls without other comorbidities.

The coronary dimensions of the patients with A-V fistula showed larger dimensions. These observations in the coronary arteries were made by echocardiographic evaluation (figure 5 lower panel and figure 8). The mean age of the patients was 54±9 yrs. (median 53; range 41,65). Other baseline characteristics of the patients are given in table 3. The mean LMCA diameter was 4.0±0.3mm,
LAD was 3.6±0.2mm, and the mean proximal RCA diameter was 3.3±0.3mm; in the control patients the LMCA diameter was 3.4±0.3mm, LAD 3.2±0.2mm and RCA was 2.8±0.4mm. The values were statistically significant (p<0.05 for all). The RCA was co-dominant or dominant in all these cases. Visual assessment (i.e., eyeballing) of the coronary arteries showed a distinct increase in size of the coronary vessels. All echocardiographic measurements of the coronary arteries were performed with the same magnifications. In 16 out of the 17 cases, the coronary dimensions were elevated in varying degrees, and in one patient the coronary dimensions were not increased.

**Statistical power calculation**

Retrospective power calculations were performed based on the observed standard deviations in each category and a minimum significant increase (minimum difference) in arterial dimensions of 0.5mm. A minimum in each group to be studied based on the standard deviation was about ten patients. Hence, the study has the minimum required power for proof of concept purposes, although this is not prospective trial proof of this effect. Based on this analysis, the study results suggest further prospective evaluation may be worthwhile [6].

**Discussion**

The results presented in the study are from 3 different patient subgroups, unrelated to each other, and the studies were performed over several years. They had one aspect in common, which was the varying degrees of dilatation of coronaries, without dilatation or hypertrophy of the left ventricle. In mitral stenosis, this could be due the fall in the mean arterial pressure compared to the controls, and in other two subgroups, it is possibly related to the existing or the closed arterio-ventricular fistulas. This could be due to changes in physical mechanics or cellular signaling. A hyperdynamic circulation as the only mechanism for coronary dilatation in A-V fistula patients is unlikely, as these patients had normal chamber dimensions.

**Application of Poisueille’s equation**

Poisueille’s law states that the velocity of the steady flow of a fluid through a narrow tube varies directly as the pressure and the fourth power of the radius of the tube and inversely as the length of the tube and the coefficient of viscosity. In these three conditions in the study, the diastolic or the coronary perfusion pressure tends to be low, and the biological response is to dilate the vessels. The study shows some interesting observations on the dilated coronary arteries in specific scenarios. The controls were normal patients, and when compared to diabetic vessels these coronary dimensions would be much higher. Analysing the Poisueille’s equation a reduction in blood pressure especially in the diastolic blood pressures would increase the radius of the blood vessels in the long term [7]. The coronary arteries are usually larger than the normal in patients with aortic regurgitation where the diastolic pressures are low. However, in this condition, the aorta is often dilated and left ventricular hypertrophy is
seen. Even in other states like rheumatic mitral regurgitation the coronary arteries are dilated. However, they are often associated with left ventricular dilatation with or without hypertrophy. The aorta and left ventricles are of standard caliber in all the three study groups. Also, in chronic renal failure on dialysis, the left ventricle is often dilated with hypertrophy. The patients chosen in this study with chronic renal failure did not have either dilatation or hypertrophy of left ventricle.

A lowering of blood pressure, could orchestrate a series of translational pathways, and result in the dilatation of the coronaries. The coronary blood flow and pressures are reduced in mitral stenosis, which improves with percutaneous balloon mitral valvuloplasty [8,9]. In patients with mitral stenosis, there is hypertrophy of the right ventricle. Hence, the right coronary or the circumflex artery would tend to be larger. However, the interesting observation is that the left anterior descending artery was also dilated in spite of the smaller left ventricle usually seen in this condition.

**Cellular mechanisms**

Baroreceptors are located in the coronaries, which are similar to the baroreceptors of the aorta [10]. These baroreceptors could mediate the changes through various signaling pathways. Possibly these mediators could be vascular endothelial growth factors [11], hepatocyte growth factors [12,13] and non-canonical WNT pathways [14-17] or Mastermind proteins [18] through NOTCH signalling [19]; Hedgehog pathways [20]. Further investigations are required to identify the exact mechanism of these observations.

Growth factors such as vascular endothelial growth factors and hepatocyte growth factors are known to have a significant role in the signaling of vessel growth. There is also an interesting observation that by creating an arterio-venous fistula the progression of chronic renal failure to end-stage renal failure is delayed [21].

Hence, the formation of the arterio-venous fistula may increase the size of the coronary arteries. This could have clinical therapeutic benefits, which would be reflected by a lower incidence in coronary events. It has been observed in various studies that enhanced external counter pulsations can reduce angina in patients with refractory angina [22, 23]. The observations in this study possibly explain the variations in blood pressures induced by enhanced counter pulsations could be the mechanism for better clinical performance in these patients [24].

There is also a potential disadvantage of the formation of an arteriovenous fistula including tachycardia, which could be managed with medications. However, as observed in this study in patients with patent ductus arteriosus who underwent closure in the past the beneficial effects of an increase in the size of the coronary vessels persist for many years even after the closure of the patent ductus arteriosus. Hence, the peripheral arteriovenous fistula, which when created, could be closed later by either surgical or percutaneous methods. To reduce the complications induced by the arteriovenous fistula, the connections could be performed in distal locations, for example, in the radial/ ulnar artery instead of the proximal brachial artery.

**Mass-Energy Equivalence principle in fluids**

The traditional mass-energy equivalence principle is applicable not only in the atomic principles but also in the fluids and super-liquid quantum vacuum [25-27]. The presence of an arteriovenous fistula tends to increase the workload in the heart and the energy dissipated will reflect on the changes in the mass and the dimensions, which would be an increase in the coronary dimensions, LV mass and also the capillary density. However, these need to be studied in detail by prospective experiments and trials.

**Limitations**

The number of patients in each category is small. The incidence of normal echocardiographic findings in patients on chronic hemodialysis is rare, and also the number of patients at follow-up who remain asymptomatic several years after patent ductus arteriosus closure is also not high. Moreover, nowadays, due to early treatment by balloon mitral valvuloplasty, the number of patients treated with valve replacement for mitral stenosis is low. Hence, the principle was to recruit as large patient numbers.
as possible. Angiography during balloon mitral valvuloplasty was performed only after some initial observations of coronary dilatations. Also, in 24 cases undergoing balloon mitral valvuloplasty before 2011, the measurements of the coronaries were based on left ventricular angiogram pictures, which are not very accurate. Nevertheless, the observation was convincing, as the coronaries are dilated.

In some conditions in the study, coronary sizes were measured by echocardiography as in patients with closed patent ductus arteriosus, and in patients with renal failure on hemodialysis, which is not the gold standard to evaluate the coronary sizes. A high degree of intra and inter-observer variability was noticed for the coronary size measurements [28]. Especially when the coronary sizes are less than 3mm. However, anatomical assessment is feasible and in children with Kawasaki’s disease [29], the coronary size measurement is performed with echocardiography in many centers routinely including our institution [30]. In this study the dilated coronaries were more than 3mm. Due to ethical considerations angiography was not contemplated in these patients. Nevertheless, this is a rare and specific group of patients selected in the study, and by visual assessment the observations were outstanding. Overall, the total number of patients in each group is less, and therefore the evidence presented is not strong. Also, the study group in all the subgroups were younger than the usual age group for coronary artery disease. Hence, further studies with large numbers need to be performed, which could reveal more information.

Right heart strain

The concept of volume overload and right atrial and ventricular dilatation and RV strain and dysfunction which is progressive over time is well known [31,32]. These studies have a median follow up period of about 3.9 (IQR 2.4-6.4) years, and the incidence of RV dysfunction is about 35% [33]. The RV dysfunction is more seen in patients with brachiocephalic fistulas than in the radial venous fistulas [31]. Hence, if a peripheral arteriovenous fistula is formed for this purpose the closure time could be in the range of 1.5 to 2 years to prevent complications.

Future perspectives

The concept outlined in the study is hypothetical and further validation accurately is only possible after an animal study by creating an arteriovenous fistula, and studying the angiogram before and after the A-V fistula possibly with a long-time interval of about 6m to 1 year in large animals. Echocardiographic measurement of coronary arteries before and after the arteriovenous fistula in clinical practice can be performed, however, this method is less accurate to conclude. The effect of beta-blockers, which reduce the heart rate and blood pressure, and its impact on coronary anatomical variations need to be studied. Also, the effect of a continuous exercise program modifying the coronary sizes needs to be determined.

Conclusion

There is a possibility for a novel therapeutic method of AV fistula formation as a method to increase coronary sizes. This concept needs to be evaluated by experimental studies in animals by observing coronary dimensions before and after creating an arteriovenous fistula.

Declarations of interest

The author declares no conflicts of interest.

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Ethical considerations: Informed consent for the procedures was taken, and institutional ethical review board approved the study (pims/13012011/C1/0/G).

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The author states that he abides by the requirements for ethical publishing in biomedical journals [34].

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