A new approach for the evaluation of the severity of coarctation of the aorta using Doppler velocity index and effective orifice area: In vitro validation and clinical implications

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Abstract

Early detection and accurate estimation of COA severity are the most important predictors of successful long-term outcome. However, current clinical parameters used for the evaluation of the severity of COA have several limitations and are flow dependent. The objectives of this study are to evaluate the limitations of current existing parameters for the evaluation of the severity of coarctation of the aorta (COA) and suggest two new parameters: COA Doppler velocity index and COA effective orifice area. Three different severities of COAs were tested in a mock flow circulation model under various flow conditions and in the presence of normal and stenotic aortic valves. Catheter trans-COA pressure gradients and Doppler echocardiographic trans-COA pressure gradients were evaluated. COA Doppler velocity index was defined as the ratio of pre-COA to post-COA peak velocities measured by Doppler echocardiography. COA Doppler effective orifice area was determined using continuity equation. The results show that peak-to-peak trans-COA pressure gradient significantly increased with flow rate (from 83% to 85%). Peak Doppler pressure gradient also significantly increased with flow rate (80–85%). A stenotic or bicuspid aortic valve increased peak Doppler pressure gradient by 20–50% for a COA severity of 75%. Both COA Doppler velocity index and COA effective orifice area did not demonstrate significant flow dependence or dependence upon aortic valve condition. As a conclusion, COA Doppler velocity index and COA effective orifice area are flow independent and do not depend on aortic valve conditions. They can, then, more accurately predict the severity of COA.

1. Introduction

Coarctation of the aorta is a congenital heart disease characterized by narrowing of the isthmus zone, the section of the descending aorta distal to the left subclavian artery. COA is encountered in 0.1% of newborns (De Mey et al., 2001) and is the third most prevailing defect in infants and children (5–8% of all congenital heart disorders) (Rao, 1995). COA often coexists with aortic stenosis (AS) (between 30% and 50%) (Brickner et al., 2000; Braverman et al., 2005). Untreated COA, in adults, can result in serious complications such as left ventricular hypertrophy, rupture of the aorta and premature coronary artery disease.

The most important predictor of successful long-term outcome in patients with COA is age at time of initial repair (Cohen et al., 1989). Early detection and accurate estimation of COA severity are then of primary importance. However, arm-to-leg blood pressure difference may not accurately represent COA severity and may significantly change with flow rate (Araoz et al., 2003; Swan et al., 2003). Doppler echocardiography and MRI trans-coarctation pressure gradients (TCPGs) are also highly dependent on flow rate and on collateral blood supply (Steffens et al., 1994; Carvalho et al., 1990). Doppler echocardiography diastolic runoff, the magnitude of the antegrade diastolic flow, has also been suggested to evaluate the severity of COA. However, it is highly dependent on aortic compliance (DeGroff et al., 2003; Tacy et al., 1999). Invasively, catheter TCPGs are highly influenced by the flow rate and pressure recovery phenomena, and peak-to-peak pressure gradient also depends on compliant properties of the aorta (Kadem et al., 2006). Furthermore, using invasive cardiac catheterization might be problematic if multiple follow-up examinations after surgical repair are required knowing that recoarctation is a common occurrence (up to 40%).
after COA repair (Araoz et al., 2003; Boxer et al., 1986; Parks et al., 1995).

In summary, the existing parameters to evaluate the severity of COA have significant limitations. It is, then, difficult to accurately compare different patients with different COA severities or a same patient between different follow-ups. Therefore, there is a crucial need to introduce new parameters capable of accurately predicting the severity of COA and clinical outcomes. Our hypothesis is that a parameter like COA velocity index defined as the ratio between pre-COA velocity and COA jet velocity and defining a COA effective orifice area using continuity equation measured by Doppler echocardiography can accurately predict the severity of COA. In order to validate our hypothesis, an original in-vitro study was performed using a mock flow circulation model with different COA severities, and different aortic valve conditions under different total flow rates.

2. Methods

We designed and constructed a mock flow circulation model which consisted of a fluid reservoir, a gear pump, realistic elastic three-dimensional models of the aorta with out-of-plane curvature (including: ascending aorta, aortic branches and descending aorta), an adjustable systemic arterial resistance and compliance (Fig. 1). We fabricated elastic models of an aorta by using a multi-silicone layer method from an anatomically shaped mold reconstructed based on a data set obtained in an adult patient by magnetic resonance imaging. With the use of this technique, successive layers of silicone were applied on the mold until both radial dilatation of the proximal aorta and total arterial compliance (determined by the ratio of pulse arterial pressure over stroke volume) match physiological values. The elastic model of the aorta used in this study has a radial dilatation of the proximal aorta of 8% (physiological value around 10% (O’Rourke et al., 2008; Herment et al., 2011)) and a total arterial compliance of 1.75 ml/mmHg (physiological value 1.84 ± 0.76 ml/mmHg (Chemla et al., 1998)). The aorta does not have tapering and its diameter is 29 ± 2 mm. In this study, COA was simulated in vitro using thin rigid circular orifices (with length of 4 ± 1 mm) correctly representing a discrete COA which is one of the most common configurations of COA (Stern et al., 1991). The fluid (a mixture of 60% water and 40% glycerol, dynamic viscosity of 4 cP) is pumped from an open tank (reservoir), crosses the model of the aortic valve (bioprosthetic valve or silicone models of bicuspid and tricuspid stenoses (Blais et al., 2006)) and directed towards the arterial module. Under normal conditions (no COA) a small portion of the total flow rate (15%) is directed towards aortic arch branches. However, when a COA is present, depending on its severity, a larger portion of the total flow rate bypasses the COA (forwarded towards the aortic branches and potential collaterals) (Markl et al., 2009; Hope et al., 2010). Including aortic arch branches is essential for the investigation of COA hemodynamics and represents a significant advantage compared to previous in-vitro setups dedicated to COA (Seifert et al., 1999; De Mey et al., 2001). In this study, the proportion of the total flow directed towards aortic arch arteries was adjusted following a mathematical modeling of the flow through COA (Table 1)(Keshavarz-Motamed et al., 2011). Then, the flow in aortic arch arteries is redirected towards the main reservoir, while the flow in the descending aorta is directed towards the model of the arterial system. The compliance and the resistance of the systemic arterial system can be adjusted to ensure physiological aortic pressure waveforms. Instantaneous flow rates were measured by two electromagnetic flowmeters (Carolina Medical Electronics, East Bend, NC, USA, 600 series, accuracy of 0.1% full scale) at the level of the ascending aorta and aortic arch arteries.

The pressures in the left ventricle, aorta, upstream from the COA and downstream of COA were measured using Millar catheters (Millar Instruments, Houston, TX, USA, SPC 360S, accuracy 0.5% full scale) located 20 mm upstream of the valve, 20 mm downstream of the valve, 20 mm upstream of the COA and 20 mm downstream of COA, respectively. Pressure measurements were used to determine: peak-to-peak, mean and maximal catheter TCPGs.

Doppler echocardiographic measurements were performed using a HP Sonos 5500 ultrasound machine (Philips healthcare, Best, The Netherlands) with a probe of 2.5 MHz. The probe was positioned on the elastic aorta and the ultrasound beam was oriented towards the COA. Both pre-COA and post-COA instantaneous velocities were measured. The measurements were performed three times and averaged. Doppler echocardiographic measurements included mean (TCPGmean) and maximal (TCPGmax) trans-COA pressure gradients using simplified energy equation (the unsteady flow component and the energy losses by turbulence and friction are neglected), with considering pre-COA velocity (TCPG = 0.5j(V2 − V2) = 4jV2/C0 at and without considering pre-COA velocity (TCPG = 0.5jV2 = 4jV2) (De Mey et al., 2001). Where V is the velocity at COA vena contracta, Vr is the velocity proximal to COA, j is the blood density and the number 4 (mmHg s2/m2) is obtained by replacement of the blood density and unit conversion from Pa to mmHg. COA Doppler velocity index was defined as DVI/coa = Vmax/pre-COA/Vmax/post-COA, i.e., the ratio between upstream COA peak velocity (measured with pulsed-wave Doppler) and downstream COA peak velocity.

Table 1 Distribution of the flow rate directed toward aortic arch arteries and through COA for different severities of COA used in this study.

<table>
<thead>
<tr>
<th>COA (%)</th>
<th>Flow through COA (L/min)</th>
<th>Flow through aortic arch arteries (L/min)</th>
</tr>
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<tbody>
<tr>
<td>50</td>
<td>70% of total flow rate</td>
<td>30% of total flow rate</td>
</tr>
<tr>
<td>75</td>
<td>60% of total flow rate</td>
<td>40% of total flow rate</td>
</tr>
<tr>
<td>90</td>
<td>45% of total flow rate</td>
<td>55% of total flow rate</td>
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Fig. 1. Schematic diagram of the in vitro flow model.
velocity (measured with continuous-wave Doppler) \( (\text{Fig. 1}) \). \( \text{EOA}_{\text{COA}} = \frac{\text{SV}_{\text{COA}}}{\text{VTI}_{\text{COA}}} = \frac{\text{SV}_{\text{COA}}}{\int_0^T \text{V}_{\text{COA}} \, dt} \). Where \( \text{SV}_{\text{COA}}, \text{VTI}_{\text{COA}}, \text{V}_{\text{COA}} \) and \( T \) are stroke volume crossing the COA, velocity-time integral downstream of COA, instantaneous velocity measured by echo Doppler and systolic duration, respectively. Sensitivity and specificity analysis were performed to evaluate the accuracy of current and proposed parameters to predict COA severity (Table 2).

2.1. Experimental conditions

First, we validated the model under physiological conditions (total stroke volume: 70 ml, heart rate: 70 bpm, systolic blood pressure: 120 mmHg, diastolic blood pressure: 70 mmHg). \( \text{Fig. 2(A)} \) and \( \text{(B)} \) show the measurement of pressure waveforms in the left ventricle, ascending aorta, upstream and downstream of COA under normal condition (without COA and/or AS). Then, we examined the flow dependence of catheter and Doppler echocardiographic derived parameters with different severities of COA (50%, 75% and 90% reduction in aortic cross-sectional area), and various aortic valve conditions (normal aortic valve (valve effective orifice area = 1.8 cm\(^2\)), bicuspid AS (valve effective orifice area = 1.3 cm\(^2\)) and tricuspid AS (valve effective orifice area = 1 cm\(^2\)) under 4 different total flow rates (3, 4, 5 and 6 L/min), simulating low to high flow rate (under moderate exercise). \( \text{Fig. 2C} \) and \( \text{D} \) show an example of Doppler echocardiographic measurements. COAs were simulated using small aspect-ratio rigid circular orifices to mimic discrete COAs found in humans.

3. Results

3.1. Analysis of current methods for the evaluation of the severity of COA

3.1.1. Peak-to-peak trans-coarctation pressure gradient (PtoP TCPG)

\( \text{Fig. 3} \) demonstrates that PtoP TCPG is significantly affected by the variation of flow rate. Indeed, for a severe COA (90%), PtoP TCPG can almost vanish at low flow rate conditions (PtoP TCPG at 6 L/min: 31 mmHg vs. PtoP TCPG at 3 L/min: 5 mmHg). Under such conditions, the severe COA (90%) will almost completely be masked by a decrease in flow rate. These findings were also observed with COA severities of 50% (decrease from 9 mmHg to 1.5 mmHg) and 75% (decrease from 20 mmHg to 2.5 mmHg) (\( \text{Fig. 4(A)} \)).

\( \text{Fig. 4(B)} \) shows how aortic valve condition can affect PtoP TCPG (for simplicity, only a COA with severity of 75% is displayed). It can be noticed that whatever is aortic valve condition (normal, tricuspid AS or bicuspid AS), PtoP TCPG is significantly reduced when the total flow rate is decreased from 6 L/min to 3 L/min. Furthermore, it appears that at a specific flow rate, aortic valve condition interacts with the COA and modifies PtoP TCPG: the presence of an AS reduces the PtoP TCPG value. This effect is more significant at higher flow rate. To these effects, PtoP TCPG cannot provide an accurate evaluation of the COA severity which can also be concluded from sensitivity and specificity analysis (Table 2).

Table 2

<table>
<thead>
<tr>
<th>Diagnostic criteria for COA severity</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
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<tbody>
<tr>
<td>Peak-to-peak trans-coarctation pressure gradient (cut-off value: 20 mmHg)</td>
<td>16.6</td>
<td>100</td>
</tr>
<tr>
<td>Doppler echocardiography trans-coarctation pressure gradients (cut-off value: 20 mmHg)</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>COA Doppler velocity index (cut-off value: DVI &lt; 0.6) (suggested in the current study)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>COA effective orifice area (cut-off value: EOA &lt; 3.0 cm(^2)) (suggested in the current study)</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

\( \text{Fig. 2.} \) Unfiltered pressure wave forms obtained from \textit{in vitro} model in normal condition (without COA and/or AS): (A) left ventricle and ascending aorta (B) upstream and downstream of COA; Doppler echocardiographic measurements: (C) pulsed wave Doppler measurements (upstream from the COA), (D) continuous wave Doppler measurements (downstream of COA).
3.1.2. Doppler echocardiography trans-coarctation pressure gradients (Doppler TCPG)

Fig. 5(A) shows that peak Doppler TCPG is highly influenced by the variation of flow rate. This trend was observed for all COA severities. Interestingly, this flow dependence is more important for severe COA (90%). Indeed, peak Doppler TCPG decreased from 34 mmHg to 5 mmHg for a decrease in total flow rate from 6 L/min to 3 L/min. Under such conditions, the severity of COA...
can completely be masked due to variation of flow rate (see Table 2 for sensitivity and specificity analysis). For COA severities of 50% and 75%, the decrease in peak trans-COA pressure gradient was from 11 to 2 mmHg and from 23 to 3 mmHg, respectively (Fig. 5).

Furthermore, since peak Doppler TCPG is a function of the square of the peak trans-COA velocity, it is highly dependent on upstream conditions. This is what is highlighted in Fig. 5(B). The presence of a bicuspid or tricuspid aortic stenosis concomitant to a 75% COA can significantly modify the peak Doppler TCPG value compared to the case with normal aortic valve: the presence of a AS increase the PtoP TCPG value. This effect becomes more significant at higher flow rate. The same behavior was observed for mean Doppler TCPG with and without considering pre-COA velocity.

3.2. A new approach for evaluation of COA severity

3.2.1. COA Doppler velocity index ($DVICOA$)

Fig. 6(A) shows that $DVICOA$ is independent from variations of flow rate (for a large total range from 3 L/min to 6 L/min). Severity of COA is the only parameter determining $DVICOA$ (for 50% COA: $DVICOA=0.50 \pm 0.006$; for 75% COA: $DVICOA=0.33 \pm 0.011$ and for 90% COA: $DVICOA=0.25 \pm 0.003$). Interestingly, $DVICOA$ is also independent from upstream conditions (valve condition: tricuspid or bicuspid AS). This is illustrated in Fig. 6(B) where for a 75% COA, $DVICOA$ is $0.33 \pm 0.011$, $0.33 \pm 0.005$ and $0.33 \pm 0.006$ for no-AS, tricuspid AS, and bicuspid AS, respectively. Moreover, the same measurements were performed on asymmetric COAs and there was a very good concordance between the results for $DVICOA$ ($R=0.99$; $SEE=0.002$). Finally, the presence of COA decreases the heart rate in patients which consequently leads to an increase in aortic pressure and stroke volume (Gupta and Wiggers, 1951). In this study, we modified the heart rate and observed that the aortic pressure changed significantly. Fig. 6(C) demonstrates that $DVICOA$ is independent from heart rate conditions and its resulting variations in aortic pressure and stroke volume.

3.2.2. COA effective orifice area ($EOACOA$)

Fig. 7(A) shows that $EOACOA$ is not dependent on flow conditions for a large interval of total flow rates. $EOACOA$ is only determined by the severity of COA; 50% COA: $EOACOA=2.67 \pm 0.04 \text{ cm}^2$; 75% COA: $EOACOA=1.38 \pm 0.02 \text{ cm}^2$ and 90% COA: $EOACOA=0.91 \pm 0.02 \text{ cm}^2$. Similar to $DVICOA$, upstream conditions (valve condition: tricuspid or bicuspid AS) do not influence $EOACOA$ as shown in Fig. 7(B). This is illustrated in Fig. 7(B) for a COA with a severity of 75%: no-AS: $EOACOA=1.38 \pm 0.02 \text{ cm}^2$; tricuspid AS: $EOACOA=1.38 \pm 0.01$ and bicuspid AS: $EOACOA=1.38 \pm 0.02 \text{ cm}^2$. Furthermore, the same measurements were performed on asymmetric COAs and there was a very good correlation between the results for $EOACOA$ ($R=0.99$; $SEE=0.05 \text{ cm}^2$). Finally, Fig. 7(C) shows that the variation in heart rate and its resulting variations in aortic pressure and stroke volume do not influence $EOACOA$.

4. Discussions

The most important predictor of successful long-term outcome in patients with COA is age at the time of the initial repair (Cohen et al., 1989). As a consequence, early detection and accurate estimation of COA severity are of primary importance. Several invasive and non-invasive parameters have been suggested in order to evaluate COA severity. However, most of these parameters have limitations (see Table 3 for summary). It is important to develop simple non-invasive, and mainly flow independent, parameters allowing accurate estimation of COA severity (Table 2: $DVICOA$ and $EOACOA$ are able to correctly identify COA severity).

$DVICOA$ introduced in this study takes into account the pre-COA velocity instead of the distal abdominal velocity as used in the parameter introduced by Teien et al. (1993). The direct
The consequence of this choice is that $DVICOA$ is independent from the development of collateral flow, a common occurrence in patients with COA. It is also important to note that: (1) $DVICOA$ is analogous in its definition to the velocity ratio (peak LVOT velocity/peak aortic velocity; LVOT: left ventricle outflow tract) introduced by Chaffizadeh and Zoghbi (1991) in order to evaluate AS severity and prosthetic heart valves; (2) $DVICOA$ correlates very well (in this study: $R=0.98$) with Euler number (ratio of the pressure loss induces by the COA and the inertial force upstream from the COA) used by De Mey et al. (2001) to investigate the limitations of Doppler echocardiography in the evaluation of COA severity. The major advantage of $DVICOA$ is that it does not rely on the determination of the aortic area upstream from COA, since measuring this area using Doppler echocardiography might be difficult in vivo.

The results of this study are based on in vitro experiments; this has the advantage of allowing a closer control of the different parameters involved in the determination of COA severity. To be applicable in vivo both pre-COA and post-COA velocities have to be measured using Doppler echocardiography. Measuring post-COA velocity using continuous wave Doppler is now a clinical routine. Pre-COA velocity is less commonly measured in patients with COA, except when correcting Doppler trans-COA pressure gradients using pre-COA velocity. For this purpose, two different approaches can be considered: (1) using continuous wave Doppler measurements: by optimizing the gain and the gray scale, it is possible to obtain a Doppler signal including both pre-COA and post-COA velocities (double envelope) (Marx and Allen, 1986; Aldousany et al., 1990); (2) using pulsed wave Doppler measurements upstream from the COA (Marx and Allen, 1986; Aldousany et al., 1990).

In order to evaluate the performance of $DVICOA$ in vivo, we used the data published in two previous studies: (1) Marx and Allen (1986): prospective study of 32 patients (pre-COA velocity was not measured in 6 patients), catheter trans-COA pressure gradient included only peak-to-peak pressure gradient; (2) Aldousany et al. (1990): retrospective study of 11 patients, catheter trans-COA gradient included peak-to-peak pressure gradient, maximal instantaneous pressure gradient (not in 2 patients) and mean gradient (not in 1 patient). There was a good correlation between $DVICOA$ and peak-to-peak transvalvular pressure gradient: Aldousany et al. ($R=0.78$); Marx and Allen ($R=0.79$); both studies: ($R=0.78$). There was a moderate correlation between $DVICOA$ and catheter mean pressure gradient ($R=0.62$). This moderate correlation can be explained by the fact that $DVICOA$ is an instantaneous parameter, while mean catheter pressure gradient is a time-averaged parameter. This argument is further reinforced by considering the very good correlation between $DVICOA$ and maximal catheter instantaneous pressure gradient ($R=0.89$).

Although $DVICOA$ and $EOACOA$ behave in the same manner to determine the severity of COA, $DVICOA$ does not inform clinicians on the energy loss induced by the presence of the COA. This can be done using $EOACOA$ and aortic post-COA area. These two parameters can be used to determine an energy loss coefficient (Garcia et al., 2000).

5. Limitations of the study

The model does not consider collateral flows or aortic valve regurgitation. This however should not modify the findings since both $DVICOA$ and $EOACOA$ have been showed in this study to be flow independent. It also should be mentioned that the determination of $EOACOA$, in vitro, using Doppler echocardiography was feasible because the aortic area in the model was known. It might not be the case, in vivo, since measuring aortic area using Doppler echocardiography upstream of the COA is challenging. More accurate results for $EOACOA$ should be obtained using magnetic resonance imaging.

Fig. 7. (A) Changes in COA effective orifice area as a function of total flow rate for different severities of COA (50%, 75% and 90%), (B) changes in COA effective orifice area as a function of total flow rate for a fixed COA (75%) and various aortic valve conditions (normal aortic valve, bicuspid AS and tricuspid AS), (C) changes in the COA effective orifice area as a function of heart rate for a fixed COA (75%), total flow rate (5 L/min) with normal aortic valve. Note that SAP and SV are systolic aortic pressure and stroke volume, respectively.
6. Conclusions

In this study, we introduced a simple and non-invasive method based on the ratio of pre-coarctation peak velocity and post-coarctation peak velocity measured by Doppler echocardiography. This parameter does not have the limitations of the current methods used to evaluate the severity of COA. Furthermore, we suggested the determination of $EOACOA$ in order to corroborate Doppler echocardiographic measurements and to allow the determination of the energy loss induced by the COA. More in-vivo studies are still required to determine whether $DVCOA$ and $EOACOA$ are reliable in clinical practice.

Conflict of interest statement

There is no conflict of interest.

References


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| Catherter peak to peak pressure gradient | Yes | Yes | Yes | Yes |
| Catherter maximum and mean pressure gradient | Yes | No | Yes | No |
| Doppler maximum and mean pressure gradient | No | No | Yes | Yes |
| Velocity ratio (Teien et al., 1993) | No | No | Yes | Yes |
| COA Doppler velocity index (suggested in the current study) | No | No | No | No |