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学 位 論 文 題 名

Reconsidering the relationship between the Doppler-derived pressure gradients and the catheter-measured gradients of aortic valvular stenosis in the pediatric population: To what extent will the effect of pressure recovery play a role?

(小児大動脈弁狭窄症における心臓超音波ドプラー法と心臓カテーテル法による圧較差の相関の再考〜圧回復の影響はどの程度なのか?)

学位論文内容の要旨

Background and Objectives

The Doppler echocardiography derived peak instantaneous systolic pressure gradient (peak instantaneous Doppler PG), the mean pressure gradient (mean Doppler PG) and the aortic valvular area are the accepted standard for the determination of the prognosis and optimal timing of intervention in adults. These noninvasive methods were validated by catheter-measured methods; however, there is a discrepancy between the Doppler-derived pressure gradients and catheter-measured gradients. Pressure recovery, which is based on the theory of fluid dynamics, plays a role in that discrepancy. Meanwhile, the peak instantaneous Doppler PG is widely applied as the only method for the noninvasive estimation of the severity of the aortic valvular stenosis in the pediatric population. In addition, the peak-to-peak transvalvular gradient obtained by cardiac catheterization (peak-to-peak catheter PG) is the accepted standard for the determination of the prognosis and optimal timing of intervention. However, theoretically, the peak-to-peak catheter PG does not reflect the genuine hemodynamic abnormality, afterload of aortic valvular stenosis and does not correspond to the peak instantaneous Doppler PG. Therefore, the first purpose of this study was to reconsider the correlation between Doppler-derived pressure gradients and catheter-measured gradients, in order to lay the foundation of the determination of the prognosis and optimal timing of intervention. The second purpose was to investigate the effect of pressure recovery in the pediatric population.

Method

The study population included 13 patients. Cardiac catheterization and Doppler echocardiography were performed. *Doppler echocardiography*: The peak instantaneous Doppler PG was determined by measuring the highest systolic velocity and calculating a pressure gradient using the Bernoulli equation. The mean Doppler PG was calculated by averaging the instantaneous Doppler gradients throughout the ejection period. The aortic valve area (AVA_c) was calculated from the continuity equation. *Cardiac catheterization*: Left ventricular and aortic pressure was measured by catheter pullback or instantaneous measurements. The conventional calculations of the catheter measured peak instantaneous pressure gradient (peak catheter PG), mean catheter pressure gradients (mean catheter PG) were measured for comparison with the corresponding Doppler echocardiographic data. *Prediction of pressure recovery*: The recovered pressure can be estimated with the following equation based on the principles of fluid dynamics:

$$\text{Pressure recovery} = 4Vcw^2 \cdot 2\frac{\text{AVAc}}{\text{AoA}}\left(1-\frac{\text{AVAc}}{\text{AoA}}\right). [1]$$

Where V_{cw} is the maximal continuous-wave Doppler velocity across the stenosis and AoA is the cross-sectional area of the ascending aorta. The pressure recovery predicted peak instantaneous systolic pressure gradient (predicted peak instantaneous Doppler PG) is expressed by the equation:

Predicted peak instantaneous Doppler PG= peak instantaneous Doppler PG-pressure recovery.

Equation [1] was also used to calculate mean recovered pressure to correct mean Doppler gradients (predicted mean Doppler PG) by subtracting it from the conventionally obtained value.

Statistical analysis: Data are presented as the mean value ± standard deviation (SD) and the range. The correlation between Doppler-determined and catheter-measured gradients was assessed by linear regression analysis and Pearson correlation coefficients were calculated. Bland and Altman analysis was performed to analyze agreement between catheter and Doppler measurements. Values of $p<0.05$ were considered to be statistically significant.

Results

Patient characteristics: The age of the study subjects ranged from 2 years to 25 years (12.8 years ±6.4 SD). Eight patients showed mild aortic regurgitation and five patients showed mild mitral regurgitation. No patients demonstrated left ventricular pump dysfunction.

Doppler-derived pressure gradients and catheter-measured gradients:

Despite the good correlation between the Doppler-derived and catheter-measured peak instantaneous pressure gradients (R^2=0.76), the Doppler gradients overestimated the catheter gradients. The peak instantaneous Doppler PG was on average 8.5 mmHg higher than the peak catheter PG, consistent with a tendency towards overestimation. A comparison between the mean Doppler PG and the mean catheter PG showed an excellent correlation (R^2=0.96) and the mean Doppler PG was an average of only 5.7 mmHg higher than the mean catheter PG. The predicted peak instantaneous Doppler PG and the predicted mean Doppler PG correlated relatively well with catheter gradients (R^2=0.63, 0.83, respectively), and underestimated higher gradients with a slope of 0.82, 0.75, respectively. In addition, the predicted instantaneous and the predicted mean Doppler PG was an average of -9.1, -4.9 mmHg lower than the peak and mean catheter PG, respectively.

Discussion

The current study yielded two important findings in the pediatric population. First, although Doppler-derived pressure gradients overestimated catheter-measured gradients, the correlations were good. In particular, the correlation between the mean Doppler PG and the mean catheter PG was excellent and the degree of overestimation was mild. Second, Doppler-predicted catheter gradients calculated using pressure recovery underestimated catheter-measured gradients. Noninvasive precise prediction of catheter-measured gradients was difficult.

The peak-to-peak catheter PG has been the accepted standard for the determination of the prognosis and optimal timing of intervention. However, the actual hemodynamic abnormality and afterlord of aortic valvular stenosis was reflected not in the peak-to-peak catheter PG but in the peak catheter PG and the mean catheter PG. In addition, the peak catheter PG and the mean catheter PG theoretically corresponded to the peak instantaneous Doppler PG and the mean Doppler PG, respectively.

Doppler-derived pressure gradients overestimated catheter-measured gradients in the current study. Next reason has been proposed to account for this overestimation. Similar to the findings in the adult population, pressure recovery occurring downstream of the vena contracta leads to an inherently different gradient than what Doppler measures between the left ventricle and vena contracta.

The correlation between the Doppler-predicted catheter gradients and catheter-measured gradients in the current study was worse than the correlation between Doppler-derived pressure gradients and catheter-measured gradients. And the Doppler-predicted catheter gradients underestimated catheter-measured gradients. This result suggested that Doppler-derived pressure gradients cannot be corrected in pediatric patients based on the existing prediction method using pressure recovery. Theoretical problems are involved in the method for calculating pressure recovery. The definition of the cross-sectional area of the ascending aorta that was 10 mm distal to the sinotubular junction for the pressure recovery formula was somewhat arbitrary. There is no consensus on the actual site where the pressure is observed to fully recover.

Although the Doppler-derived pressure gradients overestimated the catheter-measured gradients, the strong correlations of those measurements in the current study indicated that Doppler-derived pressure gradients reflect the hemodynamic abnormality and afterload of aortic valvular stenosis. In particular, the mean Doppler PG was obtained easily and the excellent correlation between the mean Doppler PG and the mean catheter PG raised the possibility that the mean Doppler PG could replace the invasive method in order to determine the prognosis and optimal timing of intervention without the need for any correction by pressure recovery in the pediatric population.

Conclusion

Doppler-derived pressure gradients overestimated the catheter-measured gradients. Theoretically, such an overestimation could be corrected by pressure recovery. However, the corrected equation for that overestimation could not apply in the pediatric population. Although Doppler-derived pressure gradients overestimated catheter-measured gradients, there were strong correlations between Doppler-derived pressure gradients and catheter-measured gradients. In particular, the excellent correlation between the mean Doppler PG and the mean catheter PG raised the possibility that the mean Doppler PG could replace invasive method in order to determine the prognosis and optimal timing of intervention without any correction of the pressure recovery in the pediatric population.

学位論文審査の要旨

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(小児大動脈弁狭窄症における心臓超音波ドプラー法と心臓カテーテル法による圧較差の相関の再考～圧回復の影響はどの程度なのか？)

近年の小児における大動脈弁狭窄症では予後の評価、治療介入の決定は心臓カテーテル検査における peak-to-peak 圧較差によっている。しかし peak-to-peak 圧較差は大動脈弁狭窄症の血行動態異常を正確には反映していない。しかも非侵襲的評価法では瞬時最大圧較差が広く用いられているが、これは理論的に peak-to-peak 圧較差に対応しない。一方成人においては侵襲的評価法により理論的に対応した非侵襲的評価法が validation されており予後の評価、治療介入の決定に汎用されている。但しこの侵襲的評価法と非侵襲的評価法の間には discrepancy が有り、圧回復の影響が注目されている。そこで、大動脈弁狭窄症の血行動態異常を反映し、理論的に互いに対応した、ドプラー法と心臓カテーテル法による瞬時最大圧較差同士の相関、更に小児では検討の少ない平均圧較差同士の相関、圧回復の影響について検討した。対象は 13 例の大動脈弁狭窄症患者で年齢 12.8 歳±6.4(平均±SD)。僧帽弁閉鎖不全症 5 例、大動脈弁閉鎖不全症 8 例を認めたが全例軽度以下であった。瞬時最大圧較差についてのドプラー法とカテーテル法の相関は良かったが(R^2=0.76)、slope

は1.22とドプラー法がカテーテル法を過大評価した。平均圧較差についての相関は大変強く(R^2=0.96)、過大評価の程度もslope 1.15と小さかった。一方成人と同様の圧回復補正を行った場合、瞬時最大圧較差では補正前より相関は低下し(R^2=0.63)、今度はドプラー法がカテーテル法を過小評価した(slope 0.82)。平均圧較差でも補正前より相関は低下し(R^2=0.83)、過小評価した(slope 0.75)。小児において成人と同様の圧回復補正が成立しなかった一つの要因は大動脈径の関与があると考えられた。実験的研究により圧回復の式の中で最も影響力のある項は大動脈径であることが知られており、既知の成人での研究より、本研究の大動脈径の方が細い傾向があった。このことは圧回復の影響を大きくさせ、実際本研究でのドプラー法による圧較差に占める圧回復の割合は、既知の成人での研究における割合より大きくなった。本研究の結果は以上のように成人同様の圧回復補正は難しい事を示した一方、小児においてほとんど使用されてこなかったドプラー法による平均圧較差が、圧回復補正を行わなくても侵襲的評価法に代わり予後評価や治療介入の決定に利用できる可能性を示したものと考えられた。申請者は以上の内容の発表を行った。

この研究内容に対して松居喜郎教授から左室大動脈圧同時圧測定と非同時圧測定の差異、年齢による圧回復への影響の程度、心機能の影響について、次に筒井裕之教授から、圧回復補正による左室大動脈間圧較差の過小評価の理由、小児で成人と異なる侵襲的計測値を用いていた理由、無症状患者の手術適応をどう考えるかについて、最後に有賀正教授より、非侵襲的評価法での予後評価や治療介入決定の可能性、圧回復補正の小児への最適化の可能性についての質問があった。これに対し申請者は本研究のデータから圧回復は年齢の影響を受けやすいことや、駆出率や心拍出量からみて心機能が悪かった例は無かった事を述べた。また、歴史的な背景とその簡便さから成人と異なる評価法がとられていることや、圧回復補正後の中でも大きく過小評価をしているものに大動脈径が細い傾向があること、現状では無症状例において 50mmHg が介入のメルクマールの一つと考えている事を述べた。更に本研究の平均圧較差の相関結果から、ドプラー法による平均圧較差は予後評価、治療介入の決定に十分応用できる可能性があると考えられること、循環器分野で用いられる他の指標のように体表面積を利用した補正など、何らかの補正により圧回復の小児への最適化も可能ではないかと考えられる事を述べた。以上のように申請者は、本研究の結果に、既知の報告の結果を加味して真摯且つ妥当な回答を行った。

本研究は理論的に対応しない侵襲的評価と非侵襲的評価同士の相関を見てきた今までの小児での大動脈弁狭窄症の評価法を見直し、小児での実態がほとんど把握されていない圧回復についても検討されており、更に侵襲的評価法に代わる非侵襲的評価法による予後評価や治療介入の決定の可能性を示したものとして重要な研究と考えられる。

審査員一同は、これらの成果を高く評価し、大学院課程における研鑽や取得単位なども併せ申請者が博士（医学）の学位を受けるのに充分な資格を有するものと判定した。