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WJC covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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ORIGINAL ARTICLE

Clinical Trials Study

Delineation of epicardial stenosis in patients with microvascular disease using pressure drop coefficient: A pilot outcome study

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Author contributions: Hebbar UU, Effat MA, Peelukhana SV and Banerjee RK designed the research; Effat MA and Arif I performed the interventions; Banerjee RK assimilated the data; Hebbar UU and Peelukhana SV performed the data analysis; Hebbar UU, Effat MA, Peelukhana SV and Banerjee RK wrote the paper.

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Abstract

AIM

To investigate the patient-outcomes of newly developed pressure drop coefficient (CDP) in diagnosing epicardial stenosis (ES) in the presence of concomitant microvascular disease (MVD).

METHODS

Patients from our clinical trial were divided into two subgroups with: (1) cut-off of coronary flow reserve

(CFR) < 2.0; and (2) diabetes. First, correlations were performed for both subgroups between CDP and hyperemic microvascular resistance (HMR), a diagnostic parameter for assessing the severity of MVD. Linear regression analysis was used for these correlations. Further, in each of the subgroups, comparisons were made between fractional flow reserve (FFR) < 0.75 and CDP > 27.9 groups for assessing major adverse cardiac events (MACE: Primary outcome). Comparisons were also made between the survival curves for FFR < 0.75 and CDP > 27.9 groups. Two tailed chi-squared and Fischer's exact tests were performed for comparison of the primary outcomes, and the log-rank test was used to compare the Kaplan-Meier survival curves. $P < 0.05$ for all tests was considered statistically significant.

RESULTS

Significant linear correlations were observed between CDP and HMR for both CFR < 2.0 ($r = 0.58$, $P < 0.001$) and diabetic ($r = 0.61$, $P < 0.001$) patients. In the CFR < 2.0 subgroup, the %MACE (primary outcomes) for CDP > 27.9 group (7.7%, 2/26) was lower than FFR < 0.75 group (3/14, 21.4%); $P = 0.21$. Similarly, in the diabetic subgroup, the %MACE for CDP > 27.9 group (12.5%, 2/16) was lower than FFR < 0.75 group (18.2%, 2/11); P = 0.69. Survival analysis for CFR < 2.0 subgroup indicated better event-free survival for CDP > 27.9 group ($n = 26$) when compared with FFR < 0.75 group ($n = 14$); $P = 0.10$. Similarly, for the diabetic subgroup, CDP > 27.9 group ($n = 16$) showed higher survival times compared to FFR group ($n = 11$); $P = 0.58$.

CONCLUSION

CDP correlated significantly with HMR and resulted in better %MACE as well as survival rates in comparison to FFR. These positive trends demonstrate that CDP could be a potential diagnostic endpoint for delineating MVD with or without ES.

Key words: Fractional flow reserve; Pressure drop coefficient; Microvascular disease; Intermediate coronary stenosis; Interventional cardiology

Core tip: Fractional flow reserve (FFR), a functional diagnostic index, is currently the gold standard for decision making in the catheterization laboratory. However, FFR can be confounded by concomitant microvascular disease (MVD). In this subgroup analysis study, pressure drop coefficient (CDP) showed improved clinical outcomes for patients with MVD compared to FFR, potentially making CDP a better diagnostic endpoint compared to FFR.

Hebbar UU, Effat MA, Peelukhana SV, Arif I, Banerjee RK. Delineation of epicardial stenosis in patients with microvascular disease using pressure drop coefficient: A pilot outcome study. *World J Cardiol* 2017; 9(12): 813-821 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i12/813.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i12.813

INTRODUCTION

A persistent clinical challenge for interventional cardiologists today is the accurate assessment of intermediate coronary stenosis. While multiple quantitative anatomical methods were proposed, their applicability remains in question[1]. Functional diagnostic indices such as fractional flow reserve (FFR) and coronary flow reserve (CFR) agree well with non-invasive stress testing[2-4], although their efficacy is limited in the presence of significant microvascular disease (MVD) as FFR and CFR depend solely on either pressure or flow measurements[5,6].

Current functional diagnostic indices

FFR, the current gold standard for the functional evaluation of epicardial stenosis (ES) is defined as the ratio of distal and proximal pressures along an ES[7-9]. The parameter ranges from "0", indicating a completely blocked vessel to "1" which indicates no obstruction. Earlier clinical outcome trials have established a cut-off value of 0.75[8] for significant coronary stenosis in the presence of single-vessel disease. However, FFR suffers from limitations, such as the zero-central venous pressure assumption as well as its dependence on the patient achieving maximal hyperemia. Also, constant minimum microvascular resistance may not be achieved in the case of sub-maximal hyperemia, leading to under-estimation of pressure drop and overestimation of FFR across the lesion[10].

CFR, the flow-derived parameter is defined as the ratio of hyperemic bood flow to basal (or resting) flow. The CFR values agreed well with non-invasive stress testing at a cut-off value of 2.0[2], and CFR < 2.0 was associated with reversible myocardial perfusion defects with high sensitivity and specificity[2]. It is worth noting that while CFR can provide the combined effect of ES and MVD, it cannot differentiate between the two conditions.

Need for alternate functional indices

FFR and CFR are based solely on pressure measurements and flow measurements, respectively. Thus, both the indices can be misleading in the presence of extended MVD[5,6]. Hybrid parameters based on pressure and flow were proposed to overcome these limitations of FFR and CFR. However, such a parameter, *e.g.*, hyperemic stenosis resistance index (HSR; ratio of pressure drop across the lesion to the distal velocity)[3] evaluates only ES. On a similar note, hyperemic microvascular resistance index (HMR; ratio of mean distal pressure and distal hyperemic velocity)[11] assesses MVD only.

To simultaneously detect ES and MVD using a single parameter, we recently introduced pressure drop coefficient (CDP), a functional diagnostic index which utilizes pressure as well as flow measurements. CDP

was validated *via in vitro*[12,13] as well as *in vivo* animal studies[12-18], and could differentiate between ES and MVD. The CDP was recently employed to differentiate between degrees of stenotic severity in a patient population[19]. In order to make interventional decisions, an equivalent cut-off to FFR < 0.75 for single vessel disease was established for CDP (CDP > 27.9)[20,21] as a marker for significant ES.

Our earlier pilot clinical study[22] validated the proposed cut-off value for CDP with positive clinical outcomes associated with the CDP > 27.9 group when compared with the FFR < 0.75 group. The objective of the current study is to assess the efficacy of CDP in delineating ES within patient subgroups suffering from MVD only. Therefore, this follow-up pilot study compares the outcomes between CDP > 27.9 and FFR < 0.75 for MVD patient subgroups extracted from the complete patient data analyzed previously[22]. Accordingly, two subgroups having possible MVD were studied: One consisting of patients with abnormal CFR (CFR < 2.0), and the other consisting of patients suffering from diabetes. Both of these subgroups were correlated with possible microvascular dysfunction in literature[23-28]. Survival curves were also compared between the FFR < 0.75 and CDP > 27.9 groups for both subgroups. Additionally, CDP was correlated with HMR - another index that uses both pressure and flow measurements to evaluate MVD. This correlation was done in both subgroups to evaluate CDP's ability to delineate MVD in the presence of ES.

MATERIALS AND METHODS

Study patients

The protocol[19] for the study was approved by the institutional review board at the University of Cincinnati (UC) and Cincinnati Veteran Affairs Medical Center (CVAMC), and informed consent was obtained from all the participants. Patients who underwent exercise testing and myocardial perfusion scans were consented based on the inclusion and exclusion criteria, which are reported in detail in our earlier study for the complete patient group[22]. The study population consisted of 86 patients enrolled at the UC and CVAMC. Table 1 summarizes the clinical characteristics of the enrolled patients in the complete patient group.

Cardiac catheterization and hemodynamic measurement

Standard-of-care catheterization techniques[22] were utilized to obtain intra-coronary pressure and flow measurements across the stenosis. All signals were recorded continuously through rest, and induction as well as decline of maximal hyperemia.

CDP calculation

CDP is defined as the ratio of trans-stenotic pressure drop to distal dynamic pressure.

$$CDP = \Delta\rho/(0.5 \times \rho \times APV^2) \quad (1)$$

where, $\Delta\rho$ is the pressure drop across the lesion; the distal dynamic pressure is the product of ρ, blood density (assumed to be a constant value of 1.05 g/cm^3), the square of average peak flow velocity (APV) and a constant value of 0.5.

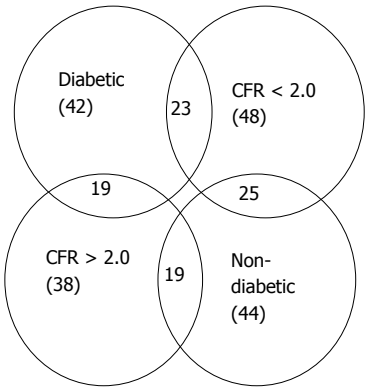

Figure 1 Overlap of the various patient subgroups. The graphic highlights the intersection of the diabetic and CFR < 2.0 patient subgroups as well as the overlap between other subgroups. CFR: Coronary flow reserve.

Patient follow-up and study endpoints

The follow-up for the consented patients was performed through either chart review, a phone call, and/or a questionnaire. A minimum of 1-year follow-up was ensured. Over the follow-up period, the primary outcomes, which consisted of major adverse cardiac events (MACE) were determined. MACE was defined as the composite of all-cause mortality, myocardial infarction (MI), and repeat revascularization (Table 2).

Sub-group methodology

In order to perform the subgroup analysis for patients suffering from possible MVD, two subgroups were extracted from the complete patient group data: One subgroup was composed of patients who exhibited an abnormal CFR value (CFR < 2.0); the other subgroup was composed of patients suffering from diabetes. Figure 1 summarizes the patient data *via* a Venn diagram showing overlap of the various patient subgroups.

Statistical analysis

The authors had sufficient prior biostatistics background, as evidenced by previous publications[19-22]. First, correlations were performed between CDP and HMR in the diabetic and CFR < 2.0 subgroups using linear regression to evaluate the agreement of CDP with HMR, a parameter reported to identify the severity of MVD.

The patient data for each subgroup was then divided per the cut-off value of FFR < 0.75 for significant ES. On a similar note, CDP > 27.9[20,21] was used as an equivalent cut-off for significant stenosis. In the primary outcome study, for each subgroup (CFR < 2.0 and diabetic), the %MACE in the FFR < 0.75 group was quantified and compared with the %MACE in the corresponding CDP > 27.9 group. All comparisons were performed using the two-tailed χ^2 test and further

Table 1 Summary of clinical data and characteristics of the recruited patients

Variable	Study/group
Sex (M/F)	77/9
Age (yr)	61 ± 9
Ejection fraction (%)	58 ± 10
Clinical history	
Diabetes	42/86
Hypertension	70/86
Dyslipidemia	60/86
Previous myocardial infarction	21/86
Smoking history	52/86
Family history of CAD	23/86
LV hypertrophy	4/86
Affected artery	
LAD	43
LCX	17
RCA	26

CAD: Coronary artery disease; LAD: Left descending artery; LCX: Left circumflex; RCA: Right coronary artery; M: Male: F: Female.

evaluated using the Fischer's exact test.

Kaplan-Meier survival curves were generated to compare the long-term event free survival of the FFR < 0.75 patient group and the CDP > 27.9 patient group. This analysis was performed for both subgroups in the study. The duration between the index procedure, and the time when the patient was last followed-up was recorded. Any patient who reached the primary outcome (MACE) was recorded as positive. Patients lost to follow-up or who did not reach the primary outcome were considered as censored data. The generated survival curves were compared using the log-rank test for statistically significant difference.

All statistical analyses were performed using MedCalc (V10.2, Mariakerke, Belgium). All results obtained were considered statistically significant if $P < 0.05$.

RESULTS

CDP was first correlated with HMR to identify its efficacy in evaluating MVD in patients suffering from concomitant ES. Further, to test the efficacy of CDP cut-off values (CDP > 27.9) as a guide for decisions on clinical intervention in patients with ES in presence of microvascular impairment, the %MACE outcomes for a CDP based strategy were statistically compared with those for a FFR based strategy (FFR < 0.75) using the two-tailed χ^2 test. The results for the Fischer's exact test were also computed to account for the lower sample size. Comparisons were performed for both subgroup methodologies: The diabetic subgroup, and the CFR < 2.0 subgroup. Further, Kaplan-Meier survival curves were generated and comparisons were made for both subgroups.

Correlation with HMR

The results for the correlation between CDP and HMR are presented in Figure 2. For the CFR < 2.0 subgroup, CDP showed a moderate but significant correlation (Figure 2A) with HMR (r = 0.58, $P < 0.001$). In the diabetic subgroup (Figure 2B), CDP again correlated moderately with HMR and the correlation was statistically significant (r = 0.61, $P < 0.001$). These results further highlight the ability of CDP to delineate severity of MVD in patients who suffer from concomitant epicardial lesions.

Table 2 Summary of the %MACE outcomes for the recruited patients at a minimum of 1-year follow-up

	FFR < 0.75	FFR > 0.75	CDP > 27.9	CDP < 27.9
CFR < 2.0				
All-cause mortality	3/14	2/34	2/26	3/22
Myocardial infarction				
Revascularization				
Diabetic				
All-cause mortality	1/11	3/31	2/16	2/26
Myocardial infarction				
Revascularization	1/11			1/26

CFR: Coronary flow reserve; CDP: Pressure drop coefficient; FFR: Fractional flow reserve.

Comparison of %MACE outcomes

The comparison of %MACE outcomes between the FFR and CDP based cut-offs for the two subgroup analyses are summarized in Figure 3. Further, the comparison performed in our earlier outcome study[22] for the complete patient group is also presented. For the CFR < 2.0 subgroup, the %MACE outcomes in the FFR < 0.75 group (3 out of 14, 21.4%) were higher than the corresponding values for the CDP > 27.9 group (7.7%, 2 out of 26) although the results were not statistically significant as per the chi-squared test ($P = 0.21$) and the Fischer's exact test ($P = 0.32$). On a similar note, for the diabetic subgroup, the %MACE in the FFR < 0.75 group (18.2%, 2 out of 11) was higher than the %MACE seen in the CDP > 27.9 group (12.5%, 2 out of 16), but the results were not statistically significant as per the chi-squared test ($P = 0.69$). The Fischer's exact test resulted in a *P*-value of 1 due to the smaller sample size. Similar to the findings in this study, the analysis performed in our earlier study[22] for the complete patient group yielded a lower %MACE outcome for the CDP > 27.9 group though the results were not significant ($P = 0.24$) for both the chi-squared test and the Fischer's exact test. These initial results suggest that if a CDP-based strategy were to be implemented, reduced %MACE outcomes would be observed when compared with the FFR-based strategy for the patient group with lower CFR values, as well as diabetic patients, who are known to suffer from MVD.

Survival analysis

Figure 4A summarizes the Kaplan-Meier survival analysis

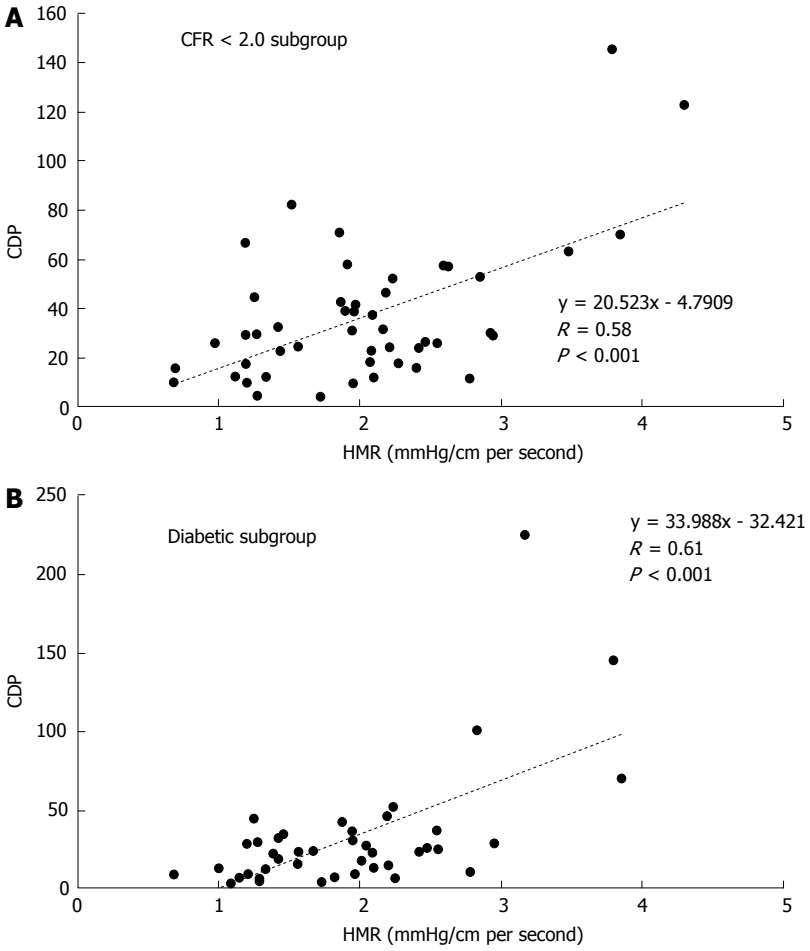

Figure 2 Correlation of pressure drop coefficient with hyperemic microvascular resistance. A: The linear regression performed between CDP and HMR for the CFR < 2.0 subgroup. The equation, *R*-value and the *P*-value are provided for the comparison; B: Similar regression performed for the diabetic subgroup. CFR: Coronary flow reserve; CDP: Pressure drop coefficient; HMR: Hyperemic microvascular resistance.

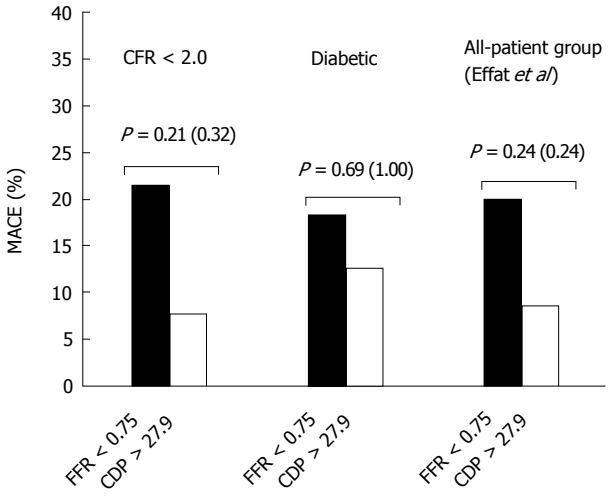

Figure 3 Comparison of %MACE between fractional flow reserve < 0.75 and pressure drop coefficient > 27.9 groups for the coronary flow reserve < 2.0 subgroup and diabetic subgroup. These patient subgroups are obtained from the complete patient group analyzed in Effat *et al*[22]. The *P*-values are provided for the χ^2 test, and the *P*-values for the Fischer's exact test are provided in parentheses. CDP: Pressure drop coefficient; FFR: Fractional flow reserve.

performed for the CFR < 2.0 subgroup. The hazard ratio was computed to be 0.26 (95%CI: 0.04-1.82) implying that the survival probability in the CDP > 27.9 group is 3.85 times the corresponding probability in the FFR < 0.75 group. The difference in survival time for the FFR < 0.75 group (n = 14) compared with the CDP > 27.9 group (n = 26) was borderline significant (P = 0.10). On a similar note, Figure 4B summarizes the survival analysis performed for the diabetic subgroup. The computed hazard ratio was 0.60 (95%CI: 0.08-4.57), indicating higher survival probability for the CDP > 27.9 group. The survival time for the FFR < 0.75 group (n = 11) was not statistically different (P = 0.58) compared to the CDP > 27.9 group (n = 16). Figure 4C shows the survival analysis performed for the complete patient group in our previous study[22]. The hazard ratio was computed to be 0.22 (95%CI: 0.06-1.24), again indicating higher survival probability for the CDP > 27.9 group. In this comparison, a statistically significant improvement in survival time for the CDP > 27.9 group was observed when compared with the FFR < 0.75 group (P = 0.048). In summary, the survival analysis indicates better survival times for the CDP > 27.9 group when compared with the FFR < 0.75 group for the complete patient group as well as for patients suffering

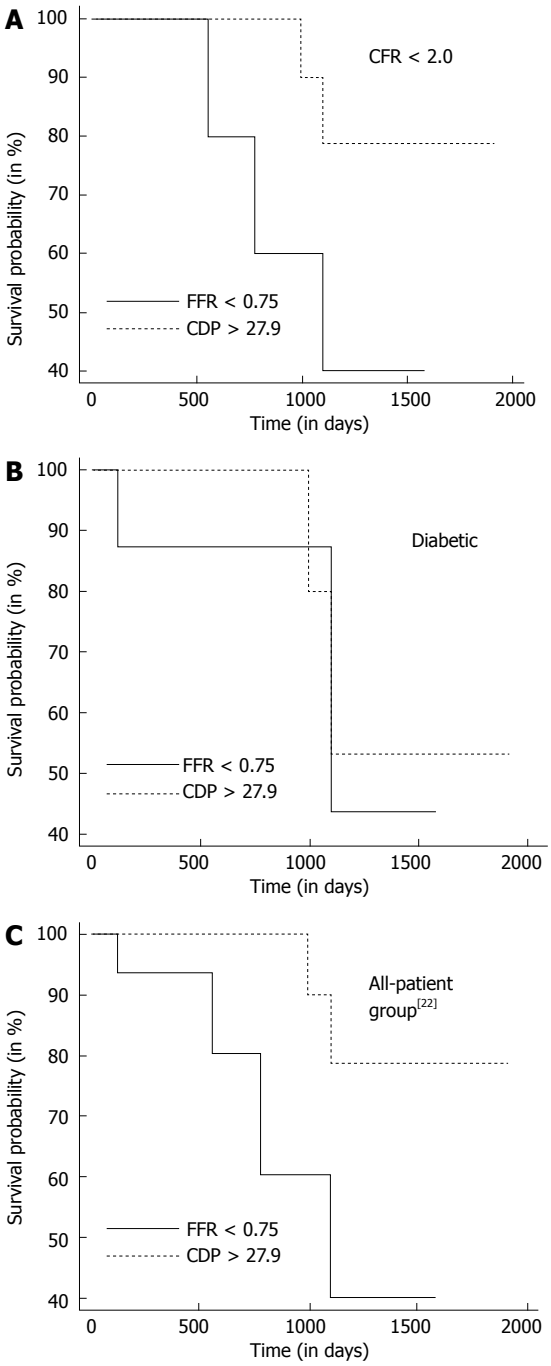

Figure 4 Comparison of Kaplan - Meier survival curves between fractional flow reserve < 0.75 and pressure drop coefficient > 27.9 groups. A: CFR < 2.0 subgroup; B: Diabetic subgroup; C: Complete patient group in Effat *et al*[22]. CFR: Coronary flow reserve; CDP: Pressure drop coefficient; FFR: Fractional flow reserve.

from MVD.

DISCUSSION

The advantages of using CDP, a combined pressure-flow diagnostic endpoint, have been reported in earlier studies[14,20-22]. However, the applicability of such a parameter in clinically relevant scenarios, particularly in the presence of MVD needs further assessment.

Correlation with HMR

HMR is a dimensional diagnostic index which utilizes pressure and flow measurements to specifically evaluate the severity of MVD in patients. In contrast, CDP is a unique non-dimensional parameter developed from fluid dynamics principles that combines pressure and flow measurements to evaluate the severity of both ES and MVD. CDP showed a moderate but significant correlation with HMR for both CFR < 2.0 and diabetic patient-subgroups, further strengthening the hypothesis that CDP can be used to evaluate the severity of MVD, with or without the presence of concomitant ES.

Comparison of %MACE outcomes

One of the significant contributors to improved quality of life is reduced incidence of MACE. Therefore, the comparison of %MACE in the FFR-based group and the CDP-based group was one of the primary results of this study. The first methodology used in the subgroup analysis was based on CFR values. It is well documented that abnormally low CFR (< 2.0) values is associated with possible MVD[23] and an inability to achieve peak hyperemia. Under this scenario, constant minimal microvascular resistance is not assured, leading to an underestimation of the pressure drop which in turn results in an overestimation of FFR values[24]. It is worth noting that in the presence of MVD and submaximal hyperemia, both blood flow as well as pressure drop over the stenosis are affected in a similar manner. Physiologically, the reduction seen in the peak hyperemic blood flow due to MVD dominates over the corresponding reduction effected by ES[14]. The formulation of CDP accounts for this effect though the square of the maximal hyperemic flow in the denominator, thus providing improved resolution for accurate evaluation of the status of the stenosis. The results for the %MACE comparisons between the FFR-based strategy and the CDP-based strategy in the study show the improved resolving power for the CDP-based patient group *via* the lower %MACE. However, considering the low rates of MACE and the relatively lower sample size in this study, a prospective randomized trial with larger patient population is required to confirm the outcomes of this pilot study.

Similar to patients with abnormal CFR, patients with diabetes are also associated with potential MVD. Previous studies of the arterioles and small arteries of diabetic patients have indicated functional microvasculature damage evidenced by reduced vasodilation of the coronary arterioles. This could be the result of a decrease in activity of ATP sensitive potassium channels[25-28]. As an additional confirmation of our hypothesis, a subsequent analysis was performed on a subgroup consisting of diabetic patients by evaluating and comparing the %MACE outcomes between the FFR-based strategy and the CDP-based strategy. The results indicated a similar trend as in the case of the CFR (< 2.0) based subgroup analysis. Additionally, the comparisons performed for the complete patient group in our previous study[22] report

similar results of reduced %MACE outcomes for the CDP group, thereby strengthening the argument that CDP can accurately delineate the status of ES, particularly in the presence of concomitant MVD. Again, these results require further assessment using a prospective randomized clinical trial with larger sample size.

Survival analysis

Another significant measure which affects the quality of life for patients suffering from cardiovascular disease is long-term event-free survival. Comparisons of the Kaplan-Meier survival curves using the log-rank test were performed between the FFR based group and the CDP based group for both subgroup methodologies discussed above. The results indicated improved long-term event free survival for the CDP-based groups in both the subgroup analyses. Furthermore, the survival curves comparison performed for the complete patient group in our previous study[22] indicated a significant improvement in long-term event free survival for the CDP group, lending further strength to the resolving power of CDP in diagnosing the status of ES with concomitant MVD.

Clinical advantages of CDP

CDP, a non-dimensional parameter based on fundamental fluid dynamics is defined as the ratio of coronary trans-lesional pressure drop (Δp) to the distal dynamic pressure (0.5 blood density APV2) where APV (average peak blood flow velocity) is measured during peak hyperemia. In the presence of increased microvascular resistance, FFR and CFR along an ES are affected in opposite directions. Therefore, ischemic assessment performed by measuring FFR and CFR in such a coronary artery with concomitant diseases might potentially lead to discordant results in up to 40% of the cases[29]. A possible explanation would be the presence of diffuse epicardial lesions wherein lower CFR would be observed without notable changes in FFR values. On the other hand, healthy microvasculature and auto-regulatory function could allow for normal CFR values while leading to abnormal FFR values. The complex interaction of pressure and flow seen in such scenarios may not be captured adequately by FFR or CFR alone, since these parameters depend solely on pressure and flow, respectively. In contrast, CDP is a combined physiological parameter derived from fundamental fluid dynamics principles involving both pressure and flow measurements, and can adequately distinguish between ES and MVD[20].

Considering the numerous advantages afforded by CDP, we believe that this parameter has a potentially significant role in modern clinical practice. However, it is worth mentioning that the dual-sensor wires necessary for computing CDP has not become prevalent in catheterization laboratories. Nevertheless, the use of these guidewires is expected to increase with: (1) technological advancement; and (2) mounting evidence of better clinical outcomes. This would make the measurement of functional diagnostic indices such as CDP standard-of-care with reduced complexities. Several prior studies have validated the clinical application of functional measures such as FFR in treatment of coronary stenosis. These include the DEFER study[24], the FAME trial[30] and the FAME 2 trial[31], which confirmed the role of FFR as a guide to management of coronary artery disease. This study proposes CDP as an improved measure over FFR for accurate prediction of major ischemic events as well as long-term event-free survival in the presence of confounding scenarios such as MVD. While statistical significance was not reached, consistent improved outcomes were observed over all the measures. Significant statistical significance in the comparisons may be observed on repeating the analysis for a larger patient group and longer follow-up periods.

Limitations

All the clinical decisions in this study were made based on FFR values alone. Thus, a larger sample size and a prospective randomized clinical trial is needed. This will allow improved evaluation of the performance of CDP compared to FFR under clinical settings and confirm the patient outcomes of this current cohort study.

In this follow-up pilot study to our earlier clinical trial[22], a subgroup analysis was performed with two subgroups: one consisting of patients exhibiting CFR < 2.0, and the other consisting of diabetic patients. CDP showed moderate but significant correlation with HMR in both the diabetic and CFR < 2.0 subgroups. Comparison of primary (%MACE) outcomes led to lower %MACE in the CDP > 27.9 groups in comparison to the FFR < 0.75 groups for both subgroups, although statistical significance was not reached. Further, event-free survival rates in the CDP > 27.9 group were higher when compared with the FFR < 0.75 group for both subgroups, with the difference being borderline significant for the CFR < 2.0 subgroup. Further clinical trials with a larger patient population and longer follow-up periods could validate the positive trends seen for the CDP group in this study, while proving the efficacy of CDP as a useful clinical endpoint for decision making in the cardiac catheterization laboratory.

ARTICLE HIGHLIGHTS

Research background

Accurate assessment of coronary stenosis is an important aspect of interventional cardiology. Although existing functional diagnostic indices such as fractional flow reserve (FFR) and coronary flow reserve (CFR) have been validated extensively *via* clinical trials, their efficacy is limited in the presence of concomitant microvascular disease (MVD) as they depend solely on pressure or flow measurements. This pilot study explores the efficacy of a combined pressure-flow diagnostic endpoint, pressure drop coefficient (CDP) compared to pressure-based FFR. It was hypothesized that CDP would show better clinical outcomes compared to FFR for patient subgroups with MVD.

Research motivation

Diagnosis of epicardial stenosis (ES) with concomitant MVD is a challenge with existing diagnostic indices (such as FFR, CFR) as they depend solely on

pressure or flow. Pressure-based FFR can be overestimated in the presence of concomitant MVD, leading to possible misdiagnosis of severity of the stenosis, while CFR cannot differentiate between the effects of the stenosis and MVD. There is a need for combined pressure-flow diagnostic endpoints (such as CDP) to better diagnose coronary stenosis, particularly in the presence of MVD.

Research objectives

The primary objective of this research was to compare the clinical outcomes of patients with stenosis and possible MVD evaluated using FFR and CDP. Secondly, CDP was correlated with an existing index (HMR) used to evaluate the severity of MVD. CDP showed better clinical outcomes compared to FFR, as well as longer survival times for the patients. Also, CDP showed significant correlation with HMR, validating its efficacy at evaluation of MVD. It is to be noted that larger sample sizes and a randomized clinical trial is required to further confirm the results of this exploratory pilot study.

Research methods

Patients from our clinical trial was divided into two subgroups with: (1) cut-off of CFR < 2.0; and (2) diabetes. First, correlations were performed for both subgroups between CDP and HMR, a diagnostic parameter for assessing the severity of MVD. Linear regression analysis was used for these correlations. Further, in each of the subgroups, comparisons were made between FFR < 0.75 and CDP > 27.9 groups for assessing major adverse cardiac events (MACE: primary outcome). Comparisons were also made between the survival curves for FFR < 0.75 and CDP > 27.9 groups. Two tailed chi-squared and Fischer's exact tests were performed for comparison of the primary outcomes, and the log-rank test was used to compare the Kaplan-Meier survival curves. $P < 0.05$ for all tests was considered statistically significant.

Research results

Significant linear correlations were observed between CDP and HMR for both CFR < 2.0 ($r = 0.58$, $P < 0.001$) and diabetic ($r = 0.61$, $P < 0.001$) patients. In the CFR < 2.0 subgroup, the %MACE (primary outcomes) for CDP > 27.9 group (7.7%, 2/26) was lower than FFR < 0.75 group (3/14, 21.4%); $P = 0.21$. Similarly, in the diabetic subgroup, the %MACE for CDP > 27.9 group (12.5%, 2/16) was lower than FFR < 0.75 group (18.2%, 2/11); $P = 0.69$. Survival analysis for CFR < 2.0 subgroup indicated better event-free survival for CDP > 27.9 group ($n = 26$) when compared with FFR < 0.75 group ($n = 14$); $P = 0.10$. Similarly, for the diabetic subgroup, CDP > 27.9 group ($n = 16$) showed higher survival times compared to FFR group ($n = 11$); $P = 0.58$.

Research conclusions

CDP correlated significantly with HMR and resulted in better %MACE as well as survival rates in comparison to FFR. These positive trends demonstrate that CDP could be a potential diagnostic endpoint for delineating MVD with or without ES.

Research perspectives

This study highlights the ability of CDP in delineating MVD in patients with or without ES. In this patient subgroup analysis, CDP showed better clinical outcomes and higher survival rates compared to FFR, which is the current gold standard in functional diagnosis of coronary artery disease. There is a clear need for functional diagnostic endpoints which can better evaluate ES with concomitant MVD. In future, a large scale randomized clinical trial comparing the outcomes of CDP and FFR is required.

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ORIGINAL ARTICLE

Observational Study

Endothelin-1 activation in pediatric patients undergoing surgical coarctation of the aorta repair

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Abstract

AIM

To determine endothelin-1 (ET-1) concentration before and after surgical coarctectomy and evaluate its association with left ventricular geometric change.

METHODS

A prospective, cohort study of 24 patients aged 2 d to 10 years with coarctation of the aorta undergoing surgical repair. A sub-cohort of patients with age < 1 mo was classified as "neonates". Echocardiograms were performed just prior to surgery and in the immediate post-op period to assess left ventricle mass index and relative wall thickness (RWT). Plasma ET-1 levels were assessed at both time points. Association between ET-1 levels and ventricular remodeling was assessed.

RESULTS

Patients < 1 year demonstrated higher pre-op ET-1 than post-op (2.8 pg/mL *vs* 1.9 pg/mL, $P = 0.02$). Conversely, patients > 1 year had no change in ET-1 concentration before and after surgery (1.1 *vs* 1.4, NS). Pre-op, patients < 1 year demonstrated significantly higher ET-1 than older children (2.8 *vs* 1.1, $P = 0.001$). Post-op there was no difference between the age groups (1.9 *vs* 1.4, NS). Neither RWT nor left ventricle mass index (LVMI) varied from pre-op to post-op. The subset of neonates showed a strong positive correlation between pre-op ET-1 and RWT ($r = 0.92$, $P = 0.001$). Patients with ET-1 > 2 pg/mL pre-op demonstrated higher LVMI (65.7 g/m$^{2.7}$ *vs* 38.5 g/m$^{2.7}$, $P = 0.004$) and a trend towards higher RWT (45% *vs* 39%, $P = 0.07$) prior to repair than those with lower ET-1 concentration.

CONCLUSION

ET-1 concentration is significantly variable in the peri-operative period surrounding coarctectomy. Older children and infants have different responses to surgical repair suggesting different mechanisms of activation.

Key words: Biomarkers; Cardiac remodeling; Pediatric; Neonate; Left ventricular hypertrophy

Core tip: Patients with coarctation of the aorta are at risk for a variety of short- and long-term complications after surgical repair. Endothelin-1 (ET-1) is a peptide hormone known to cause both cardiac myocyte hypertrophy and vasoconstriction that has been linked to late ventricular hypertrophy in this population. Peri-operative endothelin concentration in this population has not been previously defined. We demonstrate that neonates with coarctation of the aorta have high pre-operative ET-1 levels that decrease post-operatively. Older coarctation patients have more modest ET-1 activation that is unchanged post-operatively. These findings suggest two distinct patterns of ET-1 activation within this population.

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INTRODUCTION

Isolated coarctation of the aorta (CoA) is found in 800 of every million live births, approximately 8% of all congenital heart disease[1]. Open surgical repair *via* thoracotomy or sternotomy is required for most patients presenting with severe obstruction. Although perioperative mortality is low in the modern era, the post-operative course is frequently complicated by either low cardiac output syndrome or recalcitrant hypertension[2,3]. Additionally, these children are at significant risk for long-term complications including persistent hypertension, a hypertensive response to exercise, altered cardiac mechanics, and left ventricular (LV) hypertrophy[4,5].

Vascular and cardiac changes are, in many cases, already present at the time of initial surgery. Pre-operatively, approximately 65% of all children with CoA will have LV hypertrophy and 33% of the subset who are diagnosed as neonates will have evidence of pulmonary hypertension[6]. Such echocardiographic evidence of physiologic derangements, present at diagnosis, suggests that there may be early activation of critical pathologic pathways. Better understanding of such pathways and their patterns of activation offers significant promise to understand the mechanisms of disease progression, improve prognostic accuracy, and guide future therapy.

Endothelin-1 (ET-1) is a 21-amino acid vasoactive peptide hormone with endocrine and paracrine effects. Previous mechanistic *in vitro* studies have demonstrated the capacity for ET-1 to cause vasoconstriction in both the pulmonary and systemic vasculature[7] as well as cardiac myocyte hypertrophy[8,9]. Additionally, a recent study showed increased ET-1 blood concentration was associated with left ventricular hypertrophy in a mouse model of coarctation of the aorta[10]. Clinical data in human subjects, however, are quite limited. While ET-1 concentration is increased compared to controls at late follow-up after coarctation repair[11], the clinical implications of this finding are yet to be evaluated. Further, no prior study has assessed either ET-1 concentration or its association with cardiovascular pathology at the time of initial surgery for CoA. While ET-1 activation is not thought to be causative of coarctation of the aorta, defining ET-1 activation in the perioperative period could offer significant insight as a marker of the variable short and long term physiologic responses to coarctation seen in this population.

Table 1 Demographics *n* (%)

Age (d)	356 (24039)
Age class	
≤ 1 yr	12 (50)
> 1 yr	12 (50)
Age class	
≤ 28 d	7 (29.2)
28 d-1 yr	5 (20.8)
> 1 yr	12 (50)
Weight preop	7.9 (3.1, 81.8)
Weight postop	8.0 (2.9, 81.8)
Race	
African American	1 (4.2)
White	20 (83.3)
Hispanic	3 (12.5)
Gender	
Male	17 (70.8)
Female	7 (29.2)

Here we present a prospective, cohort study of ET-1 concentration and pathologic myocardial remodeling both prior to surgical correction of coarctation/aortic arch obstruction and in the immediate post-operative period. We sought to define pre-operative ET-1 activation, perioperative changes in concentrations with surgical relief, and the association with early myocardial change.

MATERIALS AND METHODS

The Colorado Multiple Institution Review Board approved this study. Written informed consent was obtained from the study subjects' parents in all cases. Written assent was obtained from all subjects aged between seven years and eighteen years.

Subjects

We prospectively enrolled consecutive subjects (aged 0 to 18 years) undergoing surgical relief of coarctation of the aorta with or without associated transverse arch hypoplasia at Children's Hospital Colorado from September 2015 through January 2017. Exclusion criteria included patients with significant co-morbid heart disease, those with a prior intervention (surgical or trans-catheter) on their aortic arch, and those weighing less than 2 kg, due to limitations in acceptable sample blood volumes for research.

Clinical data

Clinical information was extracted from the electronic medical record (Epic Systems, Verona, WI). Demographic variables, peri-operative details, and key clinical variables were recorded. Study data were collected and managed using REDCap electronic data capture tools hosted at University of Colorado[12].

Laboratory data

Blood samples were obtained immediately prior to surgery and between 12-48 h post-operatively. Extracted plasma aliquots were then stored at -80 ℃ for batch analysis. ET-1 and B-type natriuretic peptide (BNP) analysis were performed by enzyme-linked immunosorbent assay (ELISA) per manufacturer's recommendations (R and D Systems, Inc. Minneapolis, MN).

Echocardiographic data

Echocardiograms were obtained immediately prior to surgical repair and between 24 and 72 h post-operatively. All images were obtained with a GE Vivid E9 or E95 machine (General Electric, Chicago, Ill). Relative wall thickness (RWT) was measured at end-diastole from the parasternal short axis view as the ratio of the sum of the posterior and septal mural thickness to the left ventricular internal end-diastolic diameter; a value of 41% is conventionally taken as the upper limit of normal for RWT[4]. LV mass was calculated by the area-length (AL) method, indexed to height$^{2.7}$, and compared to previously published normal values[13,14].

Statistical analysis

Demographics were summarized using descriptive statistics as indicated by the distribution of the data. Changes in echocardiographic indices were compared using the Signed-Rank test. Pearson's correlation test, two-sample *T*-Test, and general linear modeling compared ET-1 levels among groups and correlation with echocardiographic indices. All the statistical analyses were performed with SAS V9.4. The primary outcome for analysis was change in ET-1 concentration from the pre-operative to the post-operative sample. Other associations were tested as secondary outcomes. Statistician S Tong from University of Colorado, Denver reviewed the statistical methods of this study.

RESULTS

Twenty-four patients were enrolled in the study. Their demographics and baseline/surgical characteristics are presented in Table 1, represented as median (range) or *n* (%). Five patients, all < 1 mo in age, underwent aortic arch reconstruction on cardio-pulmonary bypass, while the other nineteen underwent coarctectomy by lateral thoracotomy without bypass. Six patients (all in the neonatal cohort) had evidence of a patent ductus arteriosus on echocardiogram and were on prostaglandin infusion at the time of repair. In each of those six patients, ductal flow was right-to-left in systole, indicating that pressure in the pulmonary artery was equal to or greater than pressure in the aorta. One patient was on continuous milrinone. No patient received an endothelin receptor antagonist during the study period.

Clinical presentation varied by age at diagnosis. Five of the neonates were diagnosed prenatally, started on prostaglandin within the first hours of life, and remained stable until repair. Two neonates presented within the first week of life with clinical evidence of decreased systemic perfusion and were medically stabilized before proceeding to operative repair. The patients between one month and one year of life had the greatest variability in

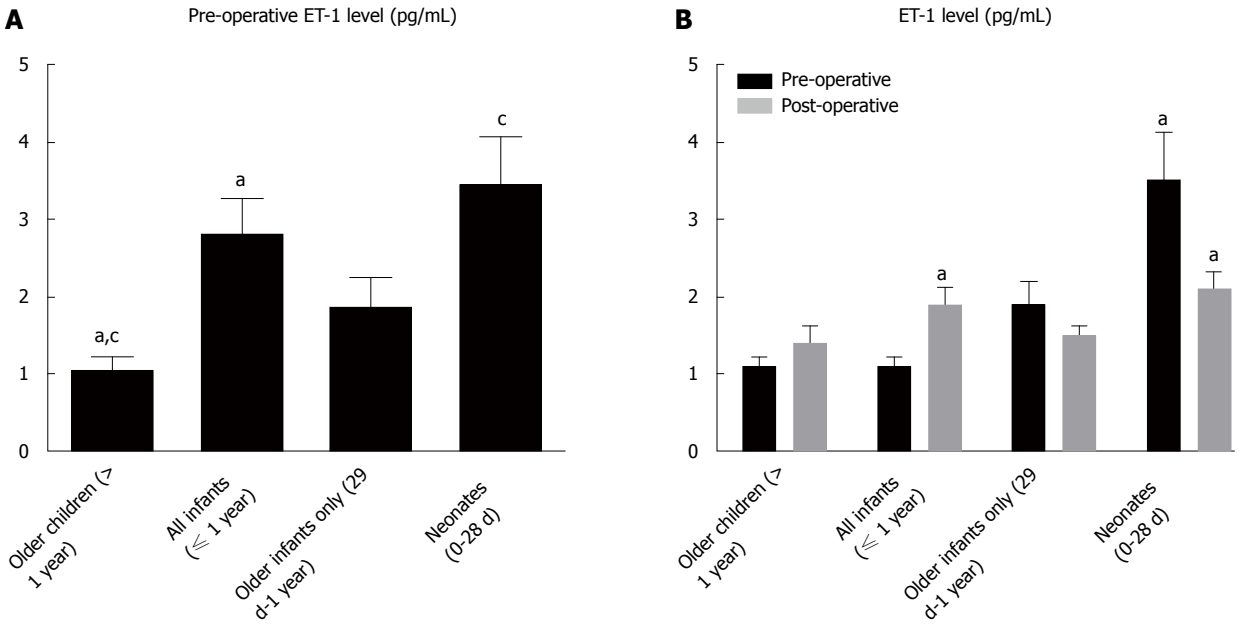

Figure 1 Serum endothelin-1 concentration. A: Pre-operative ET-1 concentration by age group; B: Comparison between pre-operative and post-operative levels for each age group. [a,c]$P < 0.05$. Scale bars represent standard deviation. ET-1: Endothelin-1.

clinical presentation, ranging from asymptomatic murmur to symptomatic left ventricular failure with decreased tissue oxygen delivery. Children older than one year were all clinically stable at presentation, referred for right upper extremity hypertension, decreased femoral pulses, or an asymptomatic murmur.

Pre-operative ET-1 concentration

Pre-op ET-1 level in our entire cohort was 1.9 pg/mL (Figure 1). Patients < 1-year-old showed significantly higher concentrations when compared to the older cohort. This effect was most pronounced among neonates, who demonstrated the highest levels.

Post-operative change in ET-1 concentration

Analysis within age cohorts demonstrated two distinct patterns. Patients < 1-year-old showed an immediate decline in ET-1 level post-op (Figure 1). Conversely, older children demonstrated no significant change between pre-op and post-op. Overall, patients with the highest levels of ET-1 pre-op demonstrated the greatest post-op decline while those with more modest ET-1 concentration pre-op tended to have unchanged levels after repair (Figure 2).

B-type natriuretic peptide concentration

For the entire population taken together, BNP concentration followed a right skewed distribution. Median pre-op BNP concentration was 73 pg/mL (upper limit of normal 99 pg/mL, range 21-4915). Neonatal subjects demonstrated significantly higher BNP levels than older children [1752 (30-4915) pg/mL *vs* 35 (21-74) pg/mL, $P < 0.0001$, represented as median (range)]. Pre-operative BNP was moderately correlated with pre-operative ET-1 ($r = 0.65$; $P = 0.0002$). Post-operatively, neonatal patients demonstrated a significant decrease in BNP level [1752 (30-4915) pg/mL *vs* 977 (192-2732) pg/mL, $P = 0.02$] while the concentration was unchanged among older children [35 (21-74) pg/mL *vs* 161 (124-451) pg/mL, NS]. Post-operative BNP was moderately correlated with post-operative ET-1 ($r = 0.73$; $P = 0.0001$).

Echocardiography

Mean RWT (%) and left ventricle mass index (LVMI) ($g/m^{2.7}$) were increased compared to normal values for all time points (Table 2). As expected, there was no significant change in RWT or LVMI between the pre-op and post-operative echocardiograms. Overall, infants showed higher LVMI compared to older children but no significant difference in RWT.

ET-1 as a biomarker of remodeling

Including the entire cohort, RWT and LVMI were compared between patients with lower and higher levels of ET-1. Patients with ET-1 > 2 pg/mL pre-op demonstrated higher LVMI (65.7 $g/m^{2.7}$ *vs* 38.5 $g/m^{2.7}$, $P = 0.004$) and a trend towards higher RWT (45% *vs* 39%, $P = 0.07$) prior to repair. Additionally, pre-op ET-1 > 2 pg/mL was associated with higher post-op LVMI and RWT. Among the neonatal cohort, pre-operative ET-1 showed a strong positive correlation with post-op RWT (Figure 2).

DISCUSSION

This study is the first to assess early ET-1 activation and its association with LV remodeling at the time of surgery for coarctation of the aorta. Key findings include increased concentration among neonates preoperatively

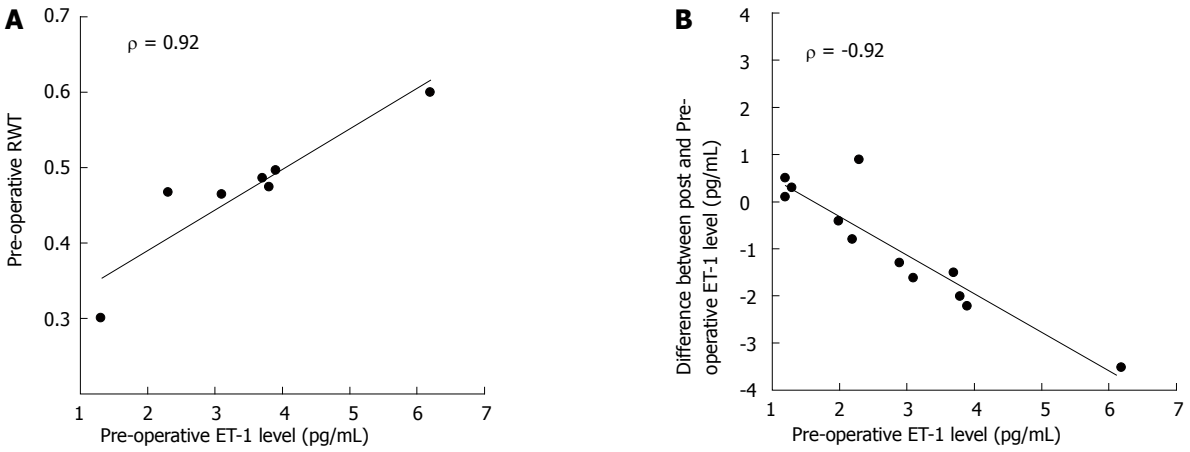

Figure 2 Pre-Operative Endothelin-1 as a predictor. A: Correlation between pre-operative ET-1 concentration and post-operative RWT in the subset cohort of neonatal patients; B: Correlation between pre-operative ET-1 concentration and change in level from pre-operative to post-operative sample in the full cohort of patients. Points represent individual patients. ET-1: Endothelin-1; RWT: Relative wall thickness.

Table 2 Echocardiographic markers of left ventricle remodeling prior to and immediately following surgical coarctectomy

	Subjects	Preop	Posop	*P* value
Relative wall thickness				
All subjects	24	0.41 (0.09)	0.42 (0.10)	NS
Neonates (0-28 d)	7	0.44 (0.09)	0.47 (0.09)	NS
Infants (29 d-1 yr)	5	0.43 (0.08)	0.40 (0.14)	NS
Children (> 1 yr)	12	0.39 (0.09)	0.39 (0.09)	NS
LV mass index				
All subjects	24	49.4 (24.6)	51.6 (17.5)	NS
Neonates (0-28 d)	7	50.2 (22.3)	57.6 (12.9)	NS
Infants (29 d-1 yr)	5	79.7 (31.1)	72.0 (19.9)	NS
Children (> 1 yr)	12	36.4 (6.3)	39.6 (7.1)	NS

LV: Left ventricle.

with a decline after anatomic correction. This pattern is contrasted with more modest ET-1 level before surgery in older children and no significant post-operative change. Taking all patients together, our population also shows higher levels of ET-1 concentration than previously reported normal controls[11]. Similar changes in ET-1 level surrounding anatomic correction of a congenital heart lesion have not previously been described. The variable pattern of ET-1 concentration seen among patients with similar anatomic lesions but different physiologies is also a novel finding.

Increasing evidence suggests that ET-1 activation is regulated in part by pulmonary vascular stress. While data conflict on whether pulmonary artery pressure or pulmonary blood flow is the primary effector, abnormalities in pulmonary vascular physiology are known to associate with alterations in serum ET-1 concentration[15-18]. Subgroup analysis of our data supports this relationship. The youngest subset of patients demonstrated the highest pre-operative ET-1 levels; these patients, in addition to manifesting high LV afterload, all demonstrated elevated pressure in the pulmonary arteries due either to ductal dependent systemic blood flow or as an upstream consequence of left atrial hypertension. Those same patients also had a post-operative decline in ET-1 level associated with the acute physiologic change (rapid normalization of pulmonary hemodynamics). The older children, with isolated high LV afterload physiology that is slower to resolve, experienced no change in ET-1 concentration from pre-op to post-op. The variable activation pattern between neonatal and older patients supports a role for the different pulmonary artery mechanics between the two subgroups affecting the variable ET-1 levels seen.

One potential confounder in the different pre-op to post-op ET-1 patterns described is the role of cardiopulmonary bypass in post-op ET-1 concentration (a majority of neonates were repaired on bypass while all older children were repaired off pump). However, prior studies of pediatric patients undergoing bypass for the Fontan operation[19] and adult patients undergoing bypass for coronary artery bypass grafting[20] have demonstrated, on average, higher plasma ET-1 concentrations after bypass. And, the two neonates who underwent coarctectomy without bypass showed the same pattern of ET-1 concentration as the rest of the neonatal cohort. The observation that patients with different pre- and post-op physiologies undergoing bypass have widely variable peri-op ET-1 concentration patterns further supports the conclusion that the peri-op physiology likely plays the dominant role in ET-1 level, rather than bypass alone.

Our data also provide preliminary evidence for a separate pathway of ET-1 regulation associated with LV afterload. All patients in our cohort, including older coarctation subjects with isolated high LV afterload and otherwise normal physiology, have higher ET-1 concentration than previously reported normal controls[11]. Previous studies have suggested such a correlation in a similar population, showing increased ET-1 levels compared to controls in hypertensive adults with high afterload physiology[21]. One possible driver of ET-1 activation in this group is sympathetic nervous system activation. Norepinephrine, an endogenous catecholamine

and effector of the sympathetic nervous system, is known both to be over-expressed in hypertensive patients[22] and to stimulate ET-1 production by the vascular endothelium[23]. Given the normal pulmonary hemodynamics in our older cohort and the mechanistic explanation offered by previous work, we posit that the ET-1 levels seen in this sub-group could reflect sympathetic activation due to the abnormality in LV and systemic vascular physiology. Future studies will be needed to confirm this hypothesis.

Individual patients who deviated from the typical clinical presentation for their age cohort provide further evidence for the two distinct mechanisms of ET-1 regulation. A neonate with a severe coarctation, acutely decreased LV function, and normal pulmonary artery pressure developed post-operative low cardiac output syndrome and his function was slow to recover. His ET-1 concentration increased slightly from the pre-operative to post-operative sample, consistent with the pattern typical of older children whose ET-1 level is likely driven by LV stress. An eight month old with severe coarctation, a dilated LV with poor systolic function, and near-systemic pulmonary artery pressure secondary to longstanding LV failure demonstrated rapidly improved pulmonary hypertension and LV function post-operatively. As would be expected, ET-1 activation in this patient more closely mirrored those in the neonatal cohort: Pre-operative ET-1 concentration was quite high and post-operative level was well below the pre-operative value.

Measured BNP concentration follows a similar trend to ET-1 concentration in this patient population. Neonatal patients have higher pre-operative BNP levels than their older counterparts and show a significant post-operative decline. Older children have lower BNP levels (normal in many cases) pre-operatively with no statistical change after surgical correction. These data suggest that neonates and some older infants experience a broad neuro-hormonal activation prior to coarctation repair in response to ventricular and potentially pulmonary artery stress and that surgical repair can result in early reversal of this neuro-hormonal activation in many patients. The specific role of BNP in this pathophysiology is not fully defined, and future studies will be needed to clarify the relationship with ET-1 and other markers of neuro-hormonal activation.

The echocardiographic data provide another layer of evidence for ET-1's potential role in the physiologic response to coarctation. Average LVMI and RWT in our patient population were significantly higher than previously published normal values and did not vary significantly through the perioperative period. This finding supports prior work demonstrating concentric LV remodeling and hypertrophy in the face of chronically high afterload with no immediate resolution following afterload reduction[6,24,25]. Mechanistically, animal studies have demonstrated that chronic ET-1 exposure induces cardiomyocyte hypertrophy *via* increased production of Extracellular Signal-Regulated Kinases 1 and 2 (ERK 1/2)[8,9,26]. Our data aligns with this finding, as patients with higher levels of ET-1 had more abnormal cardiac geometry. This novel finding combined with a biologically plausible link between ET-1 and myocyte hypertrophy raises the possibility that ET-1 could be not only a useful marker of LV remodeling but potentially an effector as well. Further, longitudinal studies will be needed to evaluate ET-1's role both in myocyte hypertrophy prior to repair and reverse remodeling after surgical correction.

In summary, we conclude that ET-1 concentration is significantly altered in patients with coarctation of the aorta undergoing surgical repair. We find preliminary evidence supporting two potentially distinct stimuli for ET-1: One mechanism, associated with high LV afterload and sympathetic nervous system activation, persists through the immediate post-operative period and the other, likely driven by altered pulmonary artery physiology, is rapidly reversible. We further find preliminary evidence supporting an association between ET-1 activity and early pathologic LV remodeling.

Limitations

This study is prospective, single center, and targets a relatively rare patient population. As such, statistical power was limited, particularly in sub-cohort analysis. Biological heterogeneity, particularly among patients between 1 mo and 1 year of age, also limited statistical analysis. Therefore, validation of these findings in similar cohorts at other centers will be of great importance. Our study design does not allow for conclusions regarding causality in the relationship between ET-1 level and LV remodeling. Due to the young age of the subject population, control serum samples for ET-1 analysis were not obtained. While historical controls from previous studies were noted for discussion, an ideal comparison including unaffected, age-matched controls will be a goal of future studies. Additionally, small patient size and safety concerns preclude routine direct clinical monitoring of pulmonary artery and left atrial pressure in the peri-operative period. While hemodynamic inferences can be drawn from available clinical data, future animal studies will be helpful to directly measure these pressures and more precisely elucidate their role in the physiology described.

ARTICLE HIGHLIGHTS

Research background

Patients with coarctation of the aorta are at risk for a variety of short- and long-term complications after surgical repair. Endothelin-1 (ET-1) is a peptide hormone known to cause both cardiac myocyte hypertrophy and vasoconstriction that has been linked to late ventricular hypertrophy in this population. Peri-operative endothelin concentration in this population has not been previously defined.

Research motivation

Defining ET-1 activation in the perioperative period could offer significant insight into the variable short and long term physiologic responses to coarctation seen in this population.

Research objectives

The authors sought to define pre-operative ET-1 activation, perioperative changes in concentrations with surgical relief, and the association with early myocardial change.

Research methods

Here authors present a prospective, cohort study of ET-1 concentration and pathologic myocardial remodeling both prior to surgical correction of coarctation/aortic arch obstruction and in the immediate post-operative period. ET-1 analysis was performed by ELISA. Echocardiograms were obtained immediately prior to surgical repair and between 24 and 72 h post-operatively. All images were obtained with a GE Vivid E9 or E95 machine (General Electric, Chicago, Ill). Relative wall thickness (RWT) was measured at end-diastole from the parasternal short axis view as the ratio of the sum of the posterior and septal mural thickness to the left ventricular internal end-diastolic diameter; a value of 41% is conventionally taken as the upper limit of normal for RWT. LV mass was calculated by the area-length (AL) method, indexed to height$^{2.7}$, and compared to previously published normal values.

Research results

The authors demonstrate that neonates with coarctation of the aorta have high pre-operative ET-1 levels that decrease post-operatively. Older coarctation patients have more modest ET-1 activation that is unchanged post-operatively.

Research conclusions

This study is the first to assess early ET-1 activation and its association with LV remodeling at the time of surgery for coarctation of the aorta. Key findings include increased concentration among neonates preoperatively with a decline after anatomic correction. This pattern is contrasted with more modest ET-1 level before surgery in older children and no significant post-operative change. The authors find preliminary evidence supporting two potentially distinct stimuli for ET-1: One mechanism, associated with high LV afterload and sympathetic nervous system activation, persists through the immediate post-operative period and the other, likely driven by altered pulmonary artery physiology, is rapidly reversible. The authors further find preliminary evidence supporting an association between ET-1 activity and early pathologic LV remodeling.

Research perspectives

Longitudinal studies will be needed to evaluate ET-1's role both in myocyte hypertrophy prior to repair and reverse remodeling after surgical correction. Given the normal pulmonary hemodynamics in the author's older cohort and the mechanistic explanation offered by previous work, the authors posit that the ET-1 levels seen in this sub-group could reflect sympathetic activation due to the abnormality in LV and systemic vascular physiology. Future studies will be needed to confirm this hypothesis. The variable activation pattern between neonatal and older patients supports a role for the different pulmonary artery mechanics between the two subgroups affecting the variable ET-1 levels seen. Further studies will be needed to clarify the role of pulmonary artery pressure and pulmonary blood flow on ET-1 concentration.

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META-ANALYSIS

Erythropoietin therapy after out-of-hospital cardiac arrest: A systematic review and meta-analysis

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Abstract

AIM

To assess safety and efficacy of early erythropoietin (Epo) administration in patients with out-of-hospital cardiac arrest (OHCA).

METHODS

A systematic literature search was performed using PubMed, MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science and Cochrane databases, of all studies published from the inception through October 10, 2016. Inclusion criteria included: (1) Adult humans with OHCA and successful sustained return of spontaneous circulation; and (2) studies including mortality/brain death, acute thrombotic events as their end points. Primary efficacy

outcome was "brain death or Cerebral Performance Category (CPC) score of 5". Secondary outcomes were "CPC score 1, and 2-4", "overall thrombotic events" and "acute coronary stent thrombosis".

RESULTS

We analyzed a total of 606 participants (n = 276 received Epo and n = 330 with standard of care alone) who experienced OHCA enrolled in 3 clinical trials. No significant difference was observed between the Epo and no Epo group in brain death or CPC score 5 (OR = 0.77; 95%CI: 0.42-1.39), CPC score 1 (OR = 1.16, 95%CI: 0.82-1.64), and CPC score 2-4 (OR = 0.77, 95%CI: 0.44-1.36). Epo group was associated with increased thrombotic complications (OR = 2.41, 95%CI: 1.26-4.62) and acute coronary stent thrombosis (OR = 8.16, 95%CI: 1.39-47.99). No publication bias was observed.

CONCLUSION

Our study demonstrates no improvement in neurological outcomes and increased incidence of thrombotic events and acute coronary stent thrombosis in OHCA patients who were treated with Epo in addition to standard therapy.

Key words: Erythropoietin; Thrombosis; Cardiac arrest; Cardiopulmonary resuscitation

Core tip: This manuscript suggested that: (1) No improvement in neurological outcomes with erythropoietin (Epo) administration after out of hospital cardiac arrest; and (2) Epo administration was also associated with increased thrombotic events and acute stent thrombosis.

Chaudhary R, Garg J, Krishnamoorthy P, Bliden K, Shah N, Agarwal N, Gupta R, Sharma A, Kern KB, Patel NC, Gurbel P. Erythropoietin therapy after out-of-hospital cardiac arrest: A systematic review and meta-analysis. *World J Cardiol* 2017; 9(12): 830-837 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i12/830.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i12.830

INTRODUCTION

Patients who undergo out-of-hospital cardiac arrest (OHCA) frequently have post-anoxic encephalopathy, even after successful initial resuscitation. This brain insult can be either transient or definitive, and is the major cause of mortality[1]. Even after successful resuscitation and restoration of cerebral perfusion, brain injury continues to progress due to reperfusion injury. At present, apart from targeted therapeutic hypothermia, no other modalities have demonstrated a reduction in cerebral anoxic brain ischemia after OHCA[2,3]. In recent years, pre-clinical studies have suggested tissue protective effects of erythropoietin (Epo) and its analogues especially after brain and myocardial damage from ischemia-reperfusion injury[4,5]. However, this did not translate into a significant clinical benefit in patients with either acute myocardial infarction or stroke[6-8]. In the setting of OHCA, there is whole body ischemia and clinical studies have shown conflicting results with 2 studies demonstrating mortality benefit with early Epo administration[9,10] and a recent randomized controlled trial with no significant benefit[11]. In view of these studies, we aim to perform a meta-analysis to assess for any significant mortality benefit of early Epo administration in patients with OHCA.

MATERIALS AND METHODS

The present review was performed according to Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements[12].

Search strategy

We carried out a literature search using PubMed, MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science and Cochrane databases, of all studies published from the inception through October 10, 2016 comparing early Epo administration in addition to standard care in patients with OHCA with standard care alone. We combined the terms ("out of hospital cardiac arrest" OR "cardiac arrest" OR "OHCA") AND ("erythropoietin" OR "EPO") as keywords or medical subject heading terms in different combinations. All references of the retrieved articles were reviewed for further identification of potentially relevant studies. The identified studies were systematically assessed using the inclusion and exclusion criteria described below.

The studies had to fulfill the following criteria to be included in the analysis: (1) adult human subjects with OHCA and successful sustained return of spontaneous circulation (ROSC); and (2) studies including mortality/brain death, acute thrombotic events as their end points. All studies with retrospective design, abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded from our analysis. Longest available follow-up data from individual studies was used for our analysis.

Data extractions and quality appraisal

Two authors (Rahul Chaudhary and Jalaj Garg) searched the studies and extracted the data independently and in duplicate. The abstractors (Jalaj Garg and Rahul Chaudhary) independently assessed the quality items, and any discrepancies were resolved by discussion and consensus with the third author (PK). Final results were reviewed by senior investigator (NP) (Figure 1).

Assessment of risk of bias for each selected study was performed according to PRISMA 2009 guidelines.

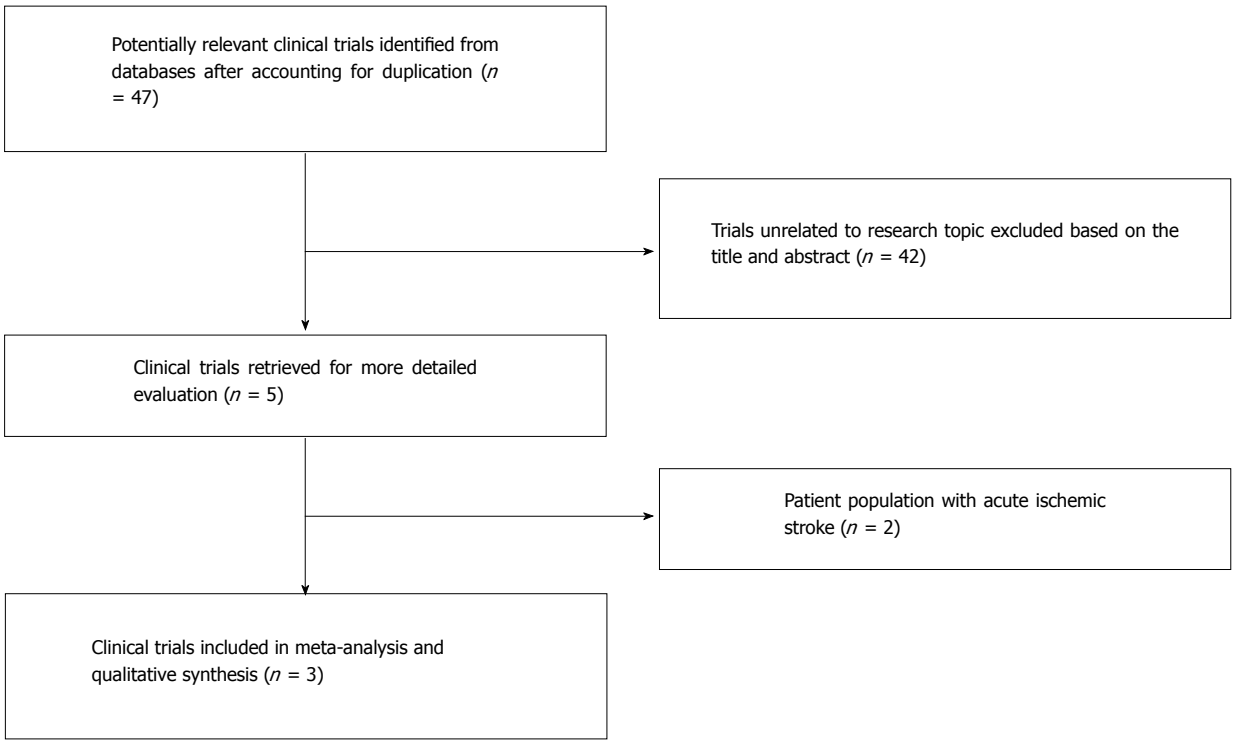

Figure 1 Process of study selection for randomized and prospective trials (PRISMA Statement).

Qualitative evaluation of bias using the following key parameters were performed for each study: (1) clear definition of study population; (2) clear definition of outcomes and outcome assessment; (3) independent assessment of outcome parameters; (4) sufficient duration of follow-up; (5) selective loss during follow-up; and (6) important confounders and prognostic factors identified. The quality of non-randomized studies were evaluated using the Newcastle-Ottawa quality assessment scale[13] and randomized controlled trials were evaluated using Cochrane Risk of Bias tool.

Outcomes

The primary efficacy outcome in our study was "brain death or Cerebral Performance Category (CPC) score of 5". Briefly, the CPC scale ranges between 1 and 5. A score of 1 represents good cerebral performance or minor disability, 2 moderate disability, 3 severe disability, 4 coma or vegetative state, and 5 represent brain death[14]. Secondary outcome assessed in our study were "CPC score 1 and 2-4", "overall thrombotic events" (defined as a combination of venous thrombosis, acute coronary stent thrombosis and other arterial thrombosis) and "acute coronary stent thrombosis".

Statistical analysis

Descriptive statistics are presented as means and SDs for continuous variables and as number of cases and percentages for dichotomous and categorical variables. Data were summarized across treatment arms using the Mantel-Haenszel odds ratio (OR) fixed effects model. Between-study heterogeneity was analyzed by means of Higgins I^2 statistic[15]. In cases of heterogeneity (defined as I^2 > 25%), random effects models of DerSimonian and Laird were used[16]. Funnel plot were evaluated visually to assess for any publication bias[17]. If any bias was observed, further bias quantification was measured using the Begg-Mazumdar Test[18], Egger Test[19] and Duval-Tweedie test[20]. The statistical analysis was performed using the Cochrane Collaborative software, RevMan 5.3.

RESULTS

A total of 47 studies were identified after exclusion of duplicate or irrelevant references (Figure 1). After detailed evaluation, 3 clinical trials (2 case-controlled studies and 1 randomized controlled study) with a total of 606 patients (276 patients received Epo in conjunction to standard of care compared to 330 patients with standard of care alone) were included in our analysis[9-11]. The characteristics of these trials and mean follow-up periods are described in Table 1.

Quality assessment and publication bias

Overall, there were clear definitions of the study population, outcomes, and assessment in the component studies. The quality assessment of individual trials is listed in Table 2. Funnel plots did not reveal publication bias for comparison of CPC score 5 and CPC score 1-4 (Figure 2).

Baseline characteristics

In the participant studies, there were no significant

Table 1 Characteristics of the included studies

Name of study	Cariou *et al*[9], 2008	Grmec *et al*[10], 2009	Cariou *et al*[11], 2016
Study design	Single center, case-control	Single center, case-control	Multicenter, single blind RCT
Total dose of Epo administered	200000 IU	90000 IU	200000 IU
Timing of Epo administration	Immediately after ROSC	Within 1 or 2 min of physician assisted CPR	Immediately after ROSC
No. of participants, *n* (intervention/control)	18/40	24/48	234/242
Mean age, yr (intervention/control)	59/58	59/60	60.5/58.6
Male gender, *n* (intervention/control)	16/39	16/34	192/184
Initial rhythm PEA/asystole, *n* (intervention/control)	2/8	12/17	94/100
Initial rhythm shockable (VF/VT), *n* (intervention/control)	16/32	12/31	115/110
Perfusing rhythm after bystander defibrillation, *n* (intervention/control)	0/0	0/0	24/31
Unknown rhythm, *n* (intervention/control)	0/0	0/0	1/3
Follow-up duration	28 d	Till hospital discharge	60 d

RCT: Randomized control trial; Epo: Erythropoietin; IU: International units; ROSC: Return of spontaneous circulation; CPR: Cardiopulmonary resuscitation; PEA: Pulseless electrical activity; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

Table 2 Assessment of quality for the included studies

Newcastle-Ottawa scale for bias assessment for case-controlled studies		
Newcastle-Ottawa scale for bias assessment	Cariou *et al*[9], 2008	Grmec *et al*[10], 2009
Selection	3	2
Comparability	2	2
Exposure	3	3
Cochrane Risk of Bias tool for the Randomized controlled study (Cariou *et al*[11])		
Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned in a 1:1 ratio to the intervention or the control group"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally with the use of a computer-generated assignment sequence Intervention assignments were made in permuted blocks of varying size and were stratified according to site"
Blinding of participants and personnel (performance bias)	High risk	Comment: Probably done Quote: "Single-blinded"; "physicians performing neurological follow-up and final outcome measurement, as well as study administrators and statisticians, were unaware of the intervention assignments" Comment: Probably done. However, only single blinding performed
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk	Quote: "Single-blinded" Comment: Probably done
Blinding of outcome assessment (detection bias) (mortality)	Low risk	Obtained from medical records; Quote "CPC was assessed by face-to-face contact with patients still hospitalized, and through phone interviews in discharged patients using a standardized protocol" Review authors do not believe this will introduce bias
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes, > 6 wk)	Low risk	60 d: 1/234 missing from intervention group ("lost to follow-up"); 0/242 missing from control group
Selective reporting (reporting bias)	Low risk	A single scale to assess neurological outcomes was used and reported (CPC score)

differences between the two groups in terms of age, gender, and initial rhythm (pulseless electrical activity or asystole and ventricular fibrillation or ventricular tachycardia). No significant heterogeneity was observed (Table 3). The mean age of our study population was 59.1 years (range 58 to 60.5 years) with 80% males.

In the component studies, standard of care included use of therapeutic hypothermia immediately upon ICU admission (or continued if initiated pre-hospital) using external or internal cooling during the first 24 h in order to obtain a target temperature between 32 ℃ and 34 ℃. Normothermia between 37 ℃ and 37.5 ℃

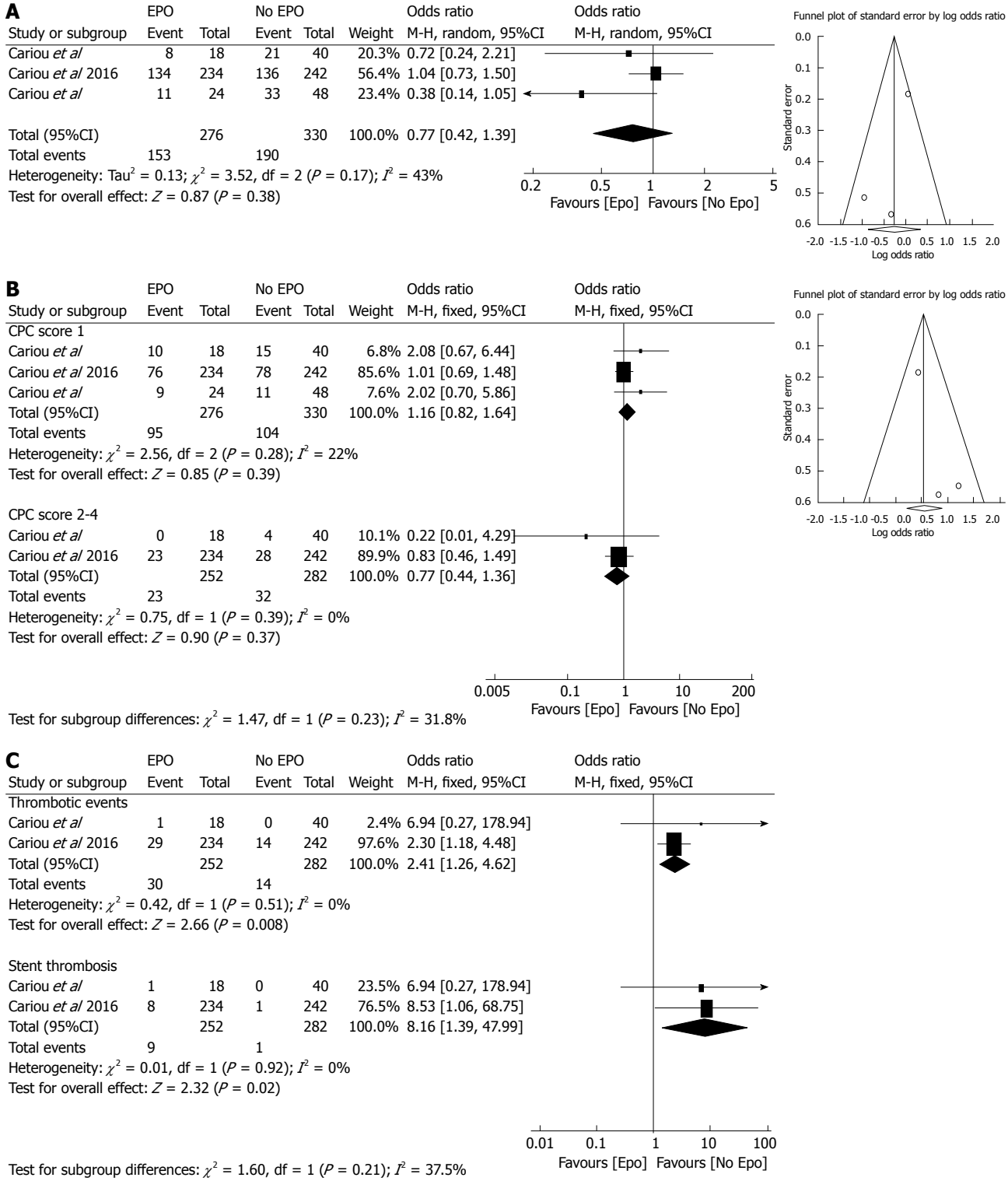

Figure 2 Forest plot demonstrating the primary and secondary outcomes in patients with out of hospital cardiac arrest who received erythropoietin compared to no erythropoietin group. A: Primary Outcomes: Brain death or CPC score 5; B: Secondary outcome: CPC score 1, and 2-4; C: Secondary outcome: Thrombotic events and acute stent thrombosis.

was then achieved using passive rewarming and maintained for the next 48 h. In patients with a high suspicion of acute coronary syndrome as the cause of OHCA, coronary angiograms were performed at hospital admission and followed by immediate percutaneous coronary interventions (PCIs) when indicated. Vasopressor agents were used, when indicated to keep the mean arterial blood pressure above 65 mmHg.

Summary of results from individual trials

In the first clinical trial evaluating use of Epo, in addition to standard therapy, for patients with OHCA, Cariou *et al*[9] showed a non-significant improvement in survival rates (55% *vs* 47.5%, *P* = 0.17) and rates of full

Table 3 Baseline demographics of study population

Baseline characteristic	Epo	No Epo	*n*	Studies (*n*)	*P* for overall effect
Age, yr	59.5	58.9	606	3	0.22
Males, %	79.2	81.4	606	3	0.93
Initial rhythm PEA/asystole, %	33.8	32.2	606	3	0.85
Initial rhythm VF/VT, %	62.7	63.3	606	3	0.45

Epo: Erythropoietin; PEA: Pulseless electrical activity; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

neurological recovery (55% *vs* 37.5%, $P > 0.05$) in a case-control study of 58 patients ($n = 18$ in Epo group and $n = 40$ in control group)[9]. In 2009, Grmec *et al*[10] showed an association of early Epo administration in patients with OHCA with higher incidence of return of spontaneous circulation (92% *vs* 71%, $P = 0.06$), 24-h survival (83% *vs* 52%, $P = 0.01$) and hospital survival (54% *vs* 31%, $P = 0.06$) in a study of 72 patients ($n = 24$ in Epo group and $n = 48$ in control group). After adjustment for pretreatment covariates all the above-mentioned outcomes were statistically significant[7]. In 2016, Cariou *et al*[11] performed a large-scale multicenter, single blind, randomized controlled trial (RCT), of 476 patients followed for a period of 60 d. They demonstrated no improvement in neurological outcomes (CPC score 1 in patients in Epo group 32.4% *vs* 43.1% in no Epo group; OR = 1.01, 95%CI: 0.68-1.48) and reported no differences between the mortality rate and proportion of patients in each CPC level between the two groups at any time points. Additionally, they observed a higher incidence of more serious adverse events with Epo administration compared to controls (22.6% *vs* 14.9%; $P = 0.03$), particularly thrombotic complications (12.4% *vs* 5.8%; $P = 0.01$)[11].

Primary outcomes

Brain death or CPC score of 5 was observed in 55% (153/276) of patients in Epo group compared to 57% (190/330) in control with no significant difference between the two groups (OR = 0.77; 95%CI: 0.42-1.39; $I^2 = 43\%$) (Figure 2A).

Secondary outcomes

No significant differences were observed between the Epo and No Epo group with CPC scores 1 (34% *vs* 31% respectively, OR = 1.16, 95%CI: 0.82-1.64; $I^2 = 22\%$), and CPC score 2-4 (9% *vs* 11% respectively; OR = 0.77, 95%CI: 0.44-1.36; $I^2 = 0\%$) (Figure 2B).

Erythropoietin therapy was associated with a significant increase in overall thrombotic events (12% *vs* 5% for Epo and control group respectively; OR = 2.41, 95%CI: 1.26-4.62; $I^2 = 0\%$) and acute coronary stent thrombosis (3% *vs* 0.3% for Epo and control group respectively; OR = 8.16, 95%CI: 1.39-47.99; $I^2 = 0\%$) (Figure 2C).

DISCUSSION

To best of our knowledge, this is the first meta-analysis comparing early use of Epo in conjunction to standard therapy with standard therapy alone in patients with out-of-hospital cardiac arrest. The major findings in our study are as follows: (1) Epo plus standard therapy was not associated with any improved neurologic recovery (brain death, *i.e.,* CPC score 5, CPC score 1-4); and (2) Epo plus standard therapy was significantly associated with increased incidence of overall thrombotic complications and acute coronary stent thrombosis.

Use of Epo as a neuroprotective agent emerged from animal models demonstrating Epo induced neuronal and vascular protection from ischemia-reperfusion injury[4,21]. Although promising, these results did not translate into improvement in clinical outcomes in patients with ischemic stroke or acute MI[6-8]. In 2008, Cariou *et al*[9] reported the first clinical study evaluating early use of Epo plus standard therapy in patients with OHCA. This study demonstrated encouraging results with a higher rate of full neurological recovery in Epo treated patients (55% *vs* 37.5%) with no significant difference mortality benefit. Similarly, Ehrenreich *et al*[7], in 2009 observed higher incidence of return of spontaneous circulation, 24-h survival and hospital survival with early administration of Epo in patients with OHCA. However, both these studies were case-control, single centered and non-randomized with a small patient population. Recently, Cariou *et al*[11] performed a large-scale multicenter, single blind, randomized controlled trial (RCT), which did not show any improvement in neurological outcomes with early administration of Epo. The results in our study are consistent with this recent RCT and other major RCTs evaluating the role of Epo in a similar setting, *i.e.,* acute MI and acute ischemic stroke[6-8]. The discrepancy between animal and human studies could be due to inter-species variability in action of Epo and mechanism of neurological injury[11].

In addition, our study demonstrated an increased incidence of overall thrombotic events and acute coronary stent thrombosis. In prior studies, Epo has been associated with increased thrombotic events including stent thrombosis in patients treated for cancer associated anemia[22] and acute myocardial infarction[6]. The underlying mechanisms involved with increased thrombogenicity with Epo in patients with OHCA remains unclear. Several mechanism have been proposed to explain stent thrombosis in patients undergoing therapeutic hypothermia - impaired drug metabolism and reduced bioavailability[23,24], increased platelet

activation[25], ineffective platelet inhibition, hypothermia induced mast cell degranulation[26]. In a recently published article from our group, we demonstrated no statistical significant difference in stent thrombosis in patients undergoing therapeutic hypothermia[27]. Also, Epo or its analogues have not been shown to enhance platelet activation[28] or activation of coagulation factors[29]. Thus it is possible increased thrombotic events in the Epo arm may be due to additional factors that were not accounted in our study (*i.e.,* erythropoietin induced increase in blood viscosity, vasoconstriction and elevated blood pressure[22,30], timing of dual antiplatelet therapy, hemodynamic circulatory support, presence of congestive heart failure, cardiogenic shock and number of stents)[27].

A major limitation of the current meta-analysis includes paucity of data from RCT's - with data from 2 case-controlled studies and only 1 RCT with a small patient population. Despite, differences in trials design, no significant heterogeneity was observed.

In conclusion, this study demonstrates no improvement in neurological outcomes and increased incidence of thrombotic events and acute coronary stent thrombosis in OHCA patients who were treated with Epo in addition to standard therapy.

ARTICLE HIGHLIGHTS

Research background

Patients with out-of-hospital cardiac arrest (OHCA) frequently have post-anoxic encephalopathy, even after successful initial resuscitation. This brain insult can be either transient or definitive, and is the major cause of mortality. Even after successful resuscitation and restoration of cerebral perfusion, brain injury continues to progress due to reperfusion injury.

Research motivation

In the setting of OHCA, there is whole body ischemia and clinical studies have shown conflicting results with 2 studies demonstrating mortality benefit with early Erythropoietin (Epo) administration and a recent randomized controlled trial with no significant benefit. In view of these studies, the authors aim to perform a meta-analysis to assess for any significant mortality benefit of early Epo administration in patients with OHCA.

Research objectives

The primary efficacy outcome in this study was "brain death or Cerebral Performance Category (CPC) score of 5". Secondary outcomes assessed in this study were "CPC scores 1 and 2-4", "overall thrombotic events" and "acute coronary stent thrombosis".

Research methods

A systematic literature search was performed using PubMed, MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science and Cochrane databases, of all studies published from the inception through October 10, 2016. The included trials were evaluated for publication bias and data summarized across treatment arms using the random effects model as odds ratio (OR).

Research results

No significant differences were observed between the two groups in brain death or CPC score of 5 (OR = 0.77; 95%CI: 0.42-1.39; I^2 = 43%), CPC score 1 (OR = 1.16, 95%CI: 0.82-1.64; I^2 = 22%), and CPC score 2-4 (OR = 0.77, 95%CI: 0.44-1.36; I^2 = 0%). Epo therapy was associated with a significant increase in overall thrombotic events (OR = 2.41, 95%CI: 1.26-4.62; I^2 = 0%) and acute coronary stent thrombosis (OR = 8.16, 95%CI: 1.39-47.99; I^2 = 0%).

Research conclusions

This study demonstrates no improvement in neurological outcomes and increased incidence of thrombotic events and acute coronary stent thrombosis in OHCA patients who were treated with Epo in addition to standard therapy.

Research perspectives

Epo administration in patients with OHCA demonstrated an increase in adverse events with no mortality benefit in addition to current standard of care. Based on the currently available literature and this systematic review, further studies are needed in order to assess the safety and efficacy of Epo in Out-Of-Cardiac-Arrest patients.

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CASE REPORT

Artefactual angulated lesion on angiography: A case report and review of literature

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Abstract

We present a case of a patient who presented with chest pain, and on diagnostic coronary angiography appeared to have a grossly angulated yet significant coronary stenosis. This was proven to be an artefactual appearance on further assessment with intravascular ultrasound imaging. We describe the causes and associations of coronary tortuosity with other arteriopathy, and highlight challenges in the interpretation of tortuous vessels to accurately assess luminal narrowing and suitability for coronary intervention. We describe a case of artefactual coronary stenosis, and its thorough assessment with intravascular ultrasound. A literature review describes the pathogenesis of coronary tortuosity, and links with other cardiovascular disease. Readers will gain an understanding of the challenge in determining the severity of luminal stenosis based on coronary angiography alone in tortuous coronary anatomy, the use of intravascular ultrasound in this setting, and the allied vasculopathies of interest.

Key words: Coronary tortuosity; Intravascular ultrasound; Spontaneous coronary artery dissection; Diagnostic coronary angiography

Core tip: Coronary arteries are inherently tortuous, and are assessed at angiography, compressing a 3D structure into a 2D picture. An overly tortuous artery may resemble true luminal stenosis, rather than mere angulation, and may be interpreted as a significant coronary stenosis. We present a remarkably angulated coronary artery, which appeared to bear a significant stenosis. On further assessment with pressure wire study and intravascular ultrasound we found there to be no significant lesion. We demonstrate an artefactual false-positive finding, and describe our clinical approach to avoid mistaking such a lesion for one that requires intervention, with a review of

the literature.

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INTRODUCTION

Coronary artery tortuosity poses many challenges in its assessment and further investigation. We present a case with ambiguous appearances at coronary angiography, clarified with intravascular imaging, and discuss the possible underpinning causes to consider when evaluating a tortuous epicardial artery.

CASE REPORT

An 80-year-old Caucasian hypertensive patient presented with atypical chest discomfort that was present both at rest and on exercise. She had no cardiovascular risk factors. She was normotensive, with BP 126/72, and heart rate 70. Her ECG was normal. Transthoracic echocardiography demonstrated preserved left ventricular function. A coronary angiogram appeared to show a severe lesion in the proximal left anterior descending coronary artery, at its origin (Figure 1). She underwent a pressure wire study to this territory, to confirm its significance, with plans to carry out further intracoronary imaging to determine whether percutaneous intervention was feasible in view of the lesion's ostial location and extreme angulation.

The pressure wire study was repeatedly negative, with instantaneous wave-free ratio of 0.97 and fractional flow reserve of 0.92 at maximal hyperaemia with systemic adenosine. Intravascular ultrasound demonstrated a normal calibre vessel throughout, with no significant atheroma seen (Video 1), contrary to the angiographic profile of the vessel.

DISCUSSION

Arteries are rarely straight, and a degree of curvature is inevitable in their path from the heart to distal tissue beds. Angulated or widespread coronary tortuosity is often seen, though its relevance is dependent on the context in which it is found, with coexistant congenital diseases and the possibility of an artefactual appearance, as described here, complicating interpretation.

Degenerative coronary tortuosity

An inordinate degree of tortuosity has been observed in ageing, hypertension, diabetes mellitus and atherosclerosis, where it may be seen in all arterial vessels, from aorta to arteriole, and throughout the venous system. Arterial tortuosity may be quantified by a number of tortuosity indices, which in general assimilate the number of curvatures of an artery away from its overall direction of travel, measured in end-diastole. Though arterial curvature is usually benign, severe tortuosity may impede blood flow in coexistant atherosclerotic disease, embolus or systemic hypoperfusion predisposing to end organ ischaemia[1].

Heritable syndromes with arterial tortuosity

Degenerative arterial tortuosity is distinct from a group of inherited arteriopathies. Extreme arterial tortuosity has been seen in a number of congenital syndromes, including Loeys-Dietz syndrome, with genetic mutations of the transforming growth factor-β receptor, Marfan Syndrome, affecting fibrillin-1, and Arterial Tortuosity Syndrome, with mutation of the SLC2A10 gene. The underlying mechanism for the effects of these deletions is unclear. They manifest as gross, diffuse arterial sinuosity affecting coronary, great vessels, carotid and vertebral arteries, and are associated with cerebrovascular infarct or aneurysm, aortic dissection and adverse overall cardiovascular outcomes[2].

Cardiovascular events in patients with coronary tortuosity

In a prospective study of coronary tortuosity in 1010 patients presenting for diagnostic coronary angiography, the incidence of epicardial coronary artery tortuosity appears to be higher in females, and its presence was correlated with hypertension yet negatively correlated with hyperlipidaemia, smoking and atherosclerosis. No significant difference was seen in major adverse cardiovascular events over a 4 year follow-up period between those with or without coronary tortuosity[3]. Conversely tortuous microvessels induce increased shear forces on blood transiting through its conduit, inducing platelet activation. This is thought to be thrombogenic, with higher mural thrombus and platelet activation seen in preclinical modelling of tortuous arterioles[4].

There appears to be an underlying genetic cause linking a continuum of arterial phenotypes from coronary tortuosity, *via* fibromuscular dysplasia and culminating in spontaneous coronary artery dissection (SCAD) with myocardial infarction. Patients with SCAD have been observed to have a high prevalence of coronary tortuosity, and this is higher still in those with recurrent SCAD. Fibromuscular dysplasia is associated with SCAD, with a recent report of *SMAD3* gene deletion underpinning a presentation of SCAD[5-7].

Challenges of assessing coronary atherosclerosis in arterial tortuosity

Native tortuosity of an epicardial coronary artery may resemble a significant luminal stenosis when straightened through passage of a guidewire. The guidewire induces a linear shape to a conduit that is normally curved, and there is invagination of the redundant tissue which impinges on the vessel lumen. This appearance disappears when the

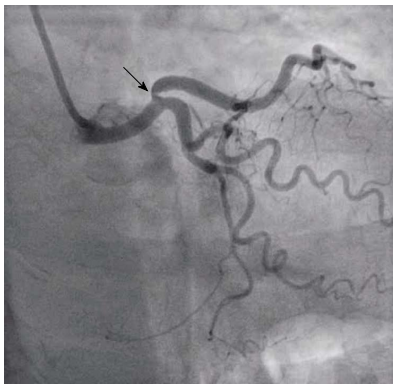

Figure 1 Artefactual angulated lesion on angiography. The coronary angiogram, shown here in the AP caudal view, appears to demonstrate a significant lesion in the proximal left anterior descending coronary artery (arrow). There was no significant impediment to flow on pressure wire study, with no significant lesion seen on intravascular ultrasound.

guidewire is retracted and the natural curvature of the vessel is restored, confirming an artefactual stenosis. This has been termed the "accordion effect". The right coronary artery has scant surrounding tissue in the atrioventricular groove in comparison to the left coronary system, and is thought to be particularly prone to this appearance with instrumentation[8]. Our case demonstrates a normal vessel lumen that appears to resemble coronary stenosis on angiographic views due to its angulation.

We demonstrate the importance of intravascular imaging in excluding a significant atherosclerotic process. The use of intravascular ultrasound has previously been described as a gold standard test, above coronary angiography, in clarifying the course of a segment of ambiguous coronary anatomy and its relationship with other vessels[9]. However these measurements are reliant on the passage of a guidewire through a curved artery, and care must be taken in intracoronary measurements in tortuous vessels. Coronary tortuosity has recently been described as a potential cause of foreshortening of vessel length in Optical Coherence Tomography (OCT), and overestimation of vessel diameter by up to 12%, due an eccentric position of the OCT catheter in a nonlinear segment of vessel, and/or the straightening effect and movement of redundant tissues as seen with the accordion effect. This effect was minimised by using a floppy rather than a stiff guidewire in this OCT study[10].

We conclude that the appearances of severe coronary stenosis in this angulated and tortuous vessel is an artefactual appearance, which was proven to have neither arteriosclerosis nor significant intraluminal narrowing on further assessment. This case highlights the importance of multimodality assessment of tortuous vessels, where luminal stenosis may be overestimated by coronary angiography. The accordion effect at coronary angiography, and underestimation of vessel length with overestimation of vessel diameter at intracoronary imaging, require careful interpretation of data for correct diagnosis. The links between coronary tortuosity and other arteriopathies are currently the subject of investigation, with a possible underpinning genetic aetiology.

ARTICLE HIGHLIGHTS

Case characteristics

The patient described atypical exertional chest pain, with no prior cardiovascular risk factors.

Clinical diagnosis

Coronary angiography initially appeared to demonstrate a severe lesion in the proximal left anterior descending coronary artery, which was demonstrated to be a false positive finding in an angulated artery with no significant coronary stenosis, through further physiological and anatomical testing.

Differential diagnosis

Further assessment of a lesion of this nature may be carried out using functional assessment, with a pressure wire study, or anatomical assessment, with intravascular ultrasound, as demonstrated here.

Imaging diagnosis

The authors used intravascular ultrasound to demonstrate a normal calibre of coronary artery. An alternative modality of optical coherence tomography may be used.

Treatment

The above approach identified a false positive finding of possible coronary stenosis, which when ruled out prevented inappropriate treatment with a coronary artery stent.

Related reports

The authors describe the aetiology of coronary angulation, which may be degenerative or heritable, and though epicardial tortuosity has not been shown to be associated with an increase in major adverse cardiovascular events an association with spontaneous coronary artery dissection, and the potential for misinterpretation of angulation as luminal stenosis, are important considerations when assessing lesions.

Experiences and lessons

The authors learned the importance of multimodality assessment of apparent coronary lesions to justify, and subsequently rule out, the need for intervention in a case of marked coronary artery curvature, and present an approach to prevent mis-interpretation.

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CASE REPORT

Successful recanalization of long femoro-crural occlusive disease after failed bypass surgery

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Abstract

Patients with critical limb ischemia necessitate immediate intervention to restore blood flow to the affected limb. Endovascular procedures are currently preferred for these patients. We describe the case of an 80-year-old female patient who presented to our department with ischemic rest pain and ulceration of the left limb. The patient had history of left femoral popliteal bypass surgery, femoral thromboendarterectomy and patch angioplasty of the same limb 2 years ago. Doppler sonography and magnetic resonance angiography revealed an occlusion of the left superficial femoral artery (SFA) and popliteal artery and of all three infra-popliteal arteries. Due to severe comorbidities, the patient was scheduled for a digital subtraction angiography. An antegrade approach was first attempted, however the occlusion could not be passed. After revision of the angiography acquisition, a stent was identified at the level of the mid SFA, which was subsequently directly punctured, facilitating the retrograde crossing of the occlusion. Thereafter, balloon angioplasty was performed in the SFA, popliteal artery and posterior tibial artery. The result was considered suboptimal, but due to the large amount of contrast agent used, a second angiography was planned in 4 wk. In the second session, drug coated balloons were used to optimize treatment of the SFA, combined with recanalization of the left fibular artery, to optimize outflow. The post-procedural course was uneventful. Ischemic pain resolved completely after the procedure and at 8 wk of follow-up and the foot ulceration completely healed.

Key words: Critical limb ischemia; Chronic occlusion; Duplex sonography; Lower limb

Core tip: Herein, we present a patient with critical ischemia of the lower limb, due to long occlusive disease of the femoro-popliteal and below-the-knee arteries who was successfully treated using an endovascular approach after failed bypass surgery and using the direct stent puncture technique. This case demonstrates that an endovascular approach may be extremely valuable even in very long, complex occlusive peripheral artery disease. This may further shift treatment from surgical to endovascular treatment in the near future.

Korosoglou G, Eisele T, Raupp D, Eisenbach C, Giusca S. Successful recanalization of long femoro-crural occlusive disease after failed bypass surgery. *World J Cardiol* 2017; 9(12): 842-847 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i12/842.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i12.842

INTRODUCTION

The prevalence and mortality of peripheral artery disease (PAD) rapidly increased during the last years due to prolonged life expectancy and is estimated to affect ⩾ 30% of older patients within the next few years[1,2]. Particularly patients with critical limb ischemia (CLI) show poor outcome with high risk for major amputation and high death rates within the first year after diagnosis[3,4]. Such patients very frequently suffer from comorbidities, like renal failure and diabetes mellitus[5] and are at high risk for septic shock if perfusion is not promptly re-established.

In patients with CLI, arterial revascularization should be performed without delay. Current guidelines provided by the task force for the treatment of PAD recommend an "endovascular first" approach in patients with CLI, taking the potential risk and the anticipated success rate of interventional treatment option into account[6]. Procedural decision should also consider the localization, complexity and length of the vascular lesions, as well as local expertise, comorbidities such as diabetes mellitus and renal failure and patients' preferences[7].

Herein, we present the case of an 80-year-old female patient with CLI due to long occlusive disease of the femoral superficial, popliteal and all 3 infra-popliteal arteries, who was successfully treated endovascularly in 2 sessions.

CASE REPORT

An 80-year-old female patient was referred to our department due to CLI with ulceration of the left limb (Rutherford Class 5), accompanied by ischemic rest pain. The patient had history of multi-vessel coronary artery disease with non-ST elevation myocardial infarction 3 mo ago. Left ventricular function was moderately reduced. In addition, she had history of arterial hypertension, hyperlipidemia, prior cigarette smoking and type 2 diabetes mellitus. Furthermore, atrial fibrillation was present. The laboratory markers showed reduced renal function with a creatinine of 1.4 mg/dL with an estimated glomerular filtration rate of GFR = 36 mL/min per 1.73 m². White blood count and C-reactive protein were increased (12300/μL and 18.3 mg/L, respectively) at the time of presentation. Clinical inspection revealed the presence of a forefoot ulcer without presence of gangrenous necrosis. The patient had history of left femoral popliteal bypass surgery as well as femoral thromboendarterectomy and patch angioplasty surgery 2 years ago. Duplex sonography relieved biphasic flow in the left iliac external and common femoral artery and a long occlusion of the femoral and popliteal artery with blunted monophasic flow in the posterior tibial artery (Figure 1A and B). No flow was present in the anterior tibial and in the fibular arteries. The ankle-brachial-index was severely reduced at 0.30. Magnetic resonance angiography (MRA) confirmed these findings, exhibiting no stenosis of the iliac arteries (Figure 1C), a long total occlusion of the left superficial femoral (SFA) (blue arrow in D showing flush occlusion of the SFA) and of the popliteal artery with collateral filling to the proximal part of the posterior tibial artery (blue arrow in Figure 1E) and occlusion of the anterior tibial, the tibiofibular tract and of the fibular artery (Figure 1D and E).

The patient had a history of chronic renal disease (creatinine = 1.4 mg/dL, GFR = 35 mL/min per 1.73 m^2), atrial fibrillation, chronic obstructive lung disease (GOLD Class 3), type 2 diabetes mellitus and multi-vessel coronary artery disease with prior non-ST elevation infarction 3 mo ago.

Due to history of failed bypass surgery and severe cardio-pulmonary comorbidities the patient was scheduled for invasive digital subtraction angiography (DSA). After inserting a 6F guiding cross-over introducer sheath (Terumo Destination®, Terumo interventional systems, Eschborn, Germany) by puncture of the right CFA, DSA confirmed flush occlusion of the left SFA (Figure 2A) with no native vessels depicted in the upper leg and in the proximal lower leg (Figure 2B and C) and with scarce filling of the posterior tibial artery (blue arrow in Figure 2D) (Video 1). Subsequently, 500 mg aspirin and 5000 IU of heparin were injected and antegrade recanalization was attempted using different hydrophilic tapered and non-tapered guidewires. However, antegrade crossing of the occlusion failed, possibly due to presence of scarred tissue in this area after surgery. After careful revision of the initial moving table non-DSA acquisition (Video 1), a stent was identified at the level of the mid SFA, which was subsequently directly punctured, facilitating the retrograde insertion of a 0.035" advantage guidewire (Terumo interventional systems, Eschborn, Germany) (Figure 2E

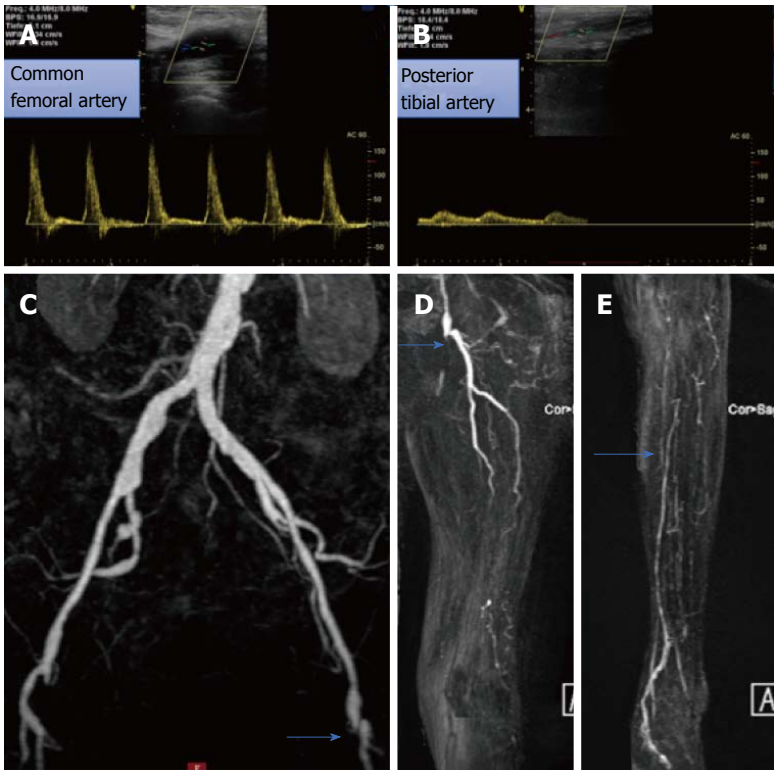

Figure 1 Duplex sonography and magnetic resonance angiography findings. A: Biphasic flow in the left common femoral artery; B: Blunted monophasic flow in the posterior tibial artery due to long occlusive disease; C: Absence of flow limiting stenosis in iliac arteries by magnetic resonance angiography; D: Long total occlusion of the SFA (blue arrow) and of the popliteal artery; E: Collateral filling in the proximal part of the posterior tibial artery (blue arrow). SFA: Superficial femoral artery.

and Video 1). Subsequently, retrograde passage of a 0.018" advantage guidewire was achieved over a 0.035" TrailBlazer support catheter, which was then snared in the 6F guiding cross-over sheath. Then, the retrograde 0.035" support catheter was pulled back and a second antegrade 0.035" support catheter was inserted over the 6F guiding cross-over sheath, which passed over the SFA through the punctured stent and was advanced to the level of the popliteal artery (blue arrow in Figure 2F). Over this 0.035" support catheter, a 0.014" advantage guidewire was advanced to the proximal anterior tibial artery and its intraluminal localization was confirmed by DSA (Figure 2G). Balloon angioplasty was then performed using a 2.5 mm × 200 mm Armada balloon (Figure 2H) in the infra-popliteal level and 5.0 mm × 200 mm and 6.0 mm × 200 mm Armada balloons (Figure 2I) (Abbott Vascular Deutschland GmbH) in the popliteal and SFA, respectively. Due to extensive dissection of the proximal SFA a 6.0 mm × 80 mm Innova self-expanding bare metal stent was placed (Boston Scientific, Ratingen, Germany). The final angiographic result, which can be depicted in Figure 2J-L was judged as suboptimal due to the absence of outflow in the lower leg. However, intervention was stopped at this point due to contrast agent administration of approximately 200 mL with chronic renal disease. The patient was put on treatment with 100 mg aspirin, 75 mg clopidogrel and 5 mg fondaparinux daily and was scheduled for re-angiography after 4 wk.

In the second session antegrade puncture of the left CFA was performed directly above the implanted stent in the proximal SFA with subsequent insertion of a short 6F guiding introducer sheath. DSA revealed moderate restenosis of the mid SFA and of the popliteal artery, which were treated using 5.0 mm × 120 mm and 6.0 mm × 120 mm Impact Pacific (Medtronic GmbH, Meerbusch, Germany) drug coated balloons, respectively. In addition, recanalization of the fibular artery was performed, resulting in functional 2 vessel out-flow of the shortly occluded posterior tibial and of the fibular artery to the left foot. Final DSA images can be appreciated in Figure 3.

The clinical course of the patient was uneventful, and she was discharged at the following day. Ischemic pain had resolved completely, and the foot ulceration healed after 3 wk. The ankle-brachial-index increased to 0.98. The patient was set on treatment with 5 mg ramipril, 20 mg atorvastatin, 5 mg bisoprolol, 75 mg clopidogrel and 15 mg rivaroxaban per day. After 8 wk, duplex sonography exhibited a well perfused SFA with biphasic flow in the distal SFA and in the popliteal artery and monophasic flow of the distal fibular and posterior tibial artery (Figure 4).

DISCUSSION

This is a case reporting on the usefulness of interventional treatment by the direct stent puncture technique in a very complex lesion with long occlusive disease of the

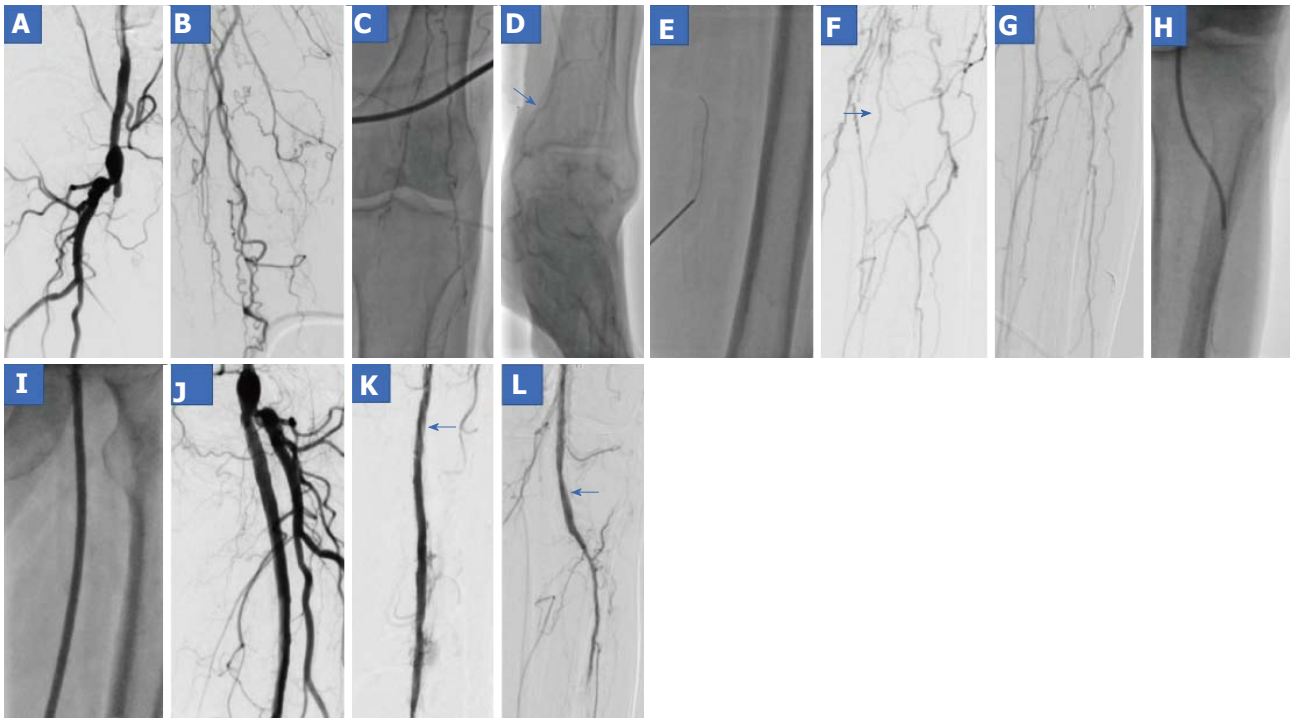

Figure 2 Digital subtraction angiography in the first interventional session. A-D: Long occlusion of the left SFA and of the popliteal artery with scarce filling of the posterior tibial artery (blue arrow in D); E: After failed antegrade crossing direct stent puncture at the level of the mid SFA was performed, achieving retrograde intraluminal passage; F: After snaring the guidewire, a 0.035" TrailBlazer support catheter was antegrade advanced to the level of the popliteal artery (blue arrow); G: A 0.014" advantage guidewire was used to wire the anterior tibial artery; H-I: Balloon angioplasty; J-L: Final angiographic result. SFA: Superficial femoral artery.

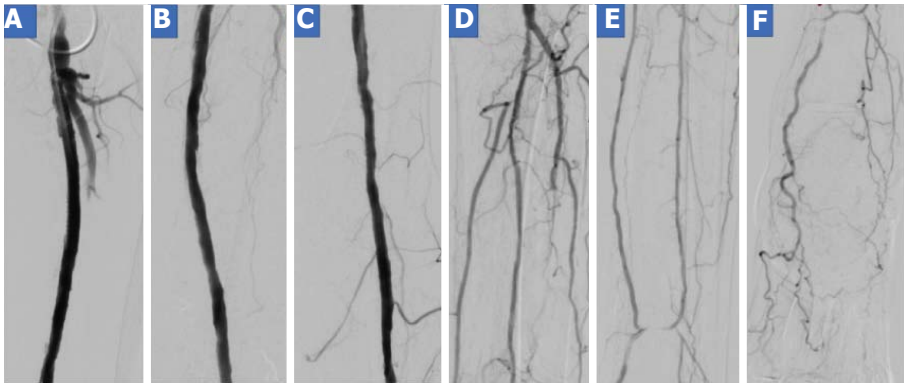

Figure 3 Digital subtraction angiography in the second interventional session. A, B: DSA images of the SFA; C: DSA image of popliteal artery; D-F: DSA images of crural and foot arteries after the second angiographic procedure. SFA: Superficial femoral artery; DSA: Digital subtraction angiography.

SFA, popliteal artery and below-the-knee arteries.

CLI is associated with high amputation and mortality rates, depending on concomitant risk factors and treatment options[8]. From a pathophysiologic point of view, ischemia of the limb is reversible, but causes irreversible tissue death, if left untreated. In patients presenting with CLI, current guidelines by the task force for the treatment of PAD recommend an "endovascular first" approach depending on the anatomy and complexity of the underlying lesions. However, with long occlusion of the SFA and popliteal artery bypass surgery should be considered due to rather poor technical success rates and high risk for re-occlusion, especially in segments with predicted poor patency rates in the distal downstream segments[7]. In our case, long femoro-popliteal occlusive disease was present along with occlusion of the proximal tibial posterior artery and total occlusion of the tibiofibular tract, of the fibular and the anterior tibial artery. Despite the complexity of the lesion, we chose an interventional approach due to failed bypass surgery and cardiac comorbidities. We used the direct stent puncture technique, which was previously described as an efficient and safe option for intraluminal stent recanalization in femoro-popliteal occlusive lesions[9,10], exhibiting high technical success rates and low rates of peri- and postprocedural complications, such as distal embolization and hematoma at the puncture site[11]. Like previously reported cases, we punctured

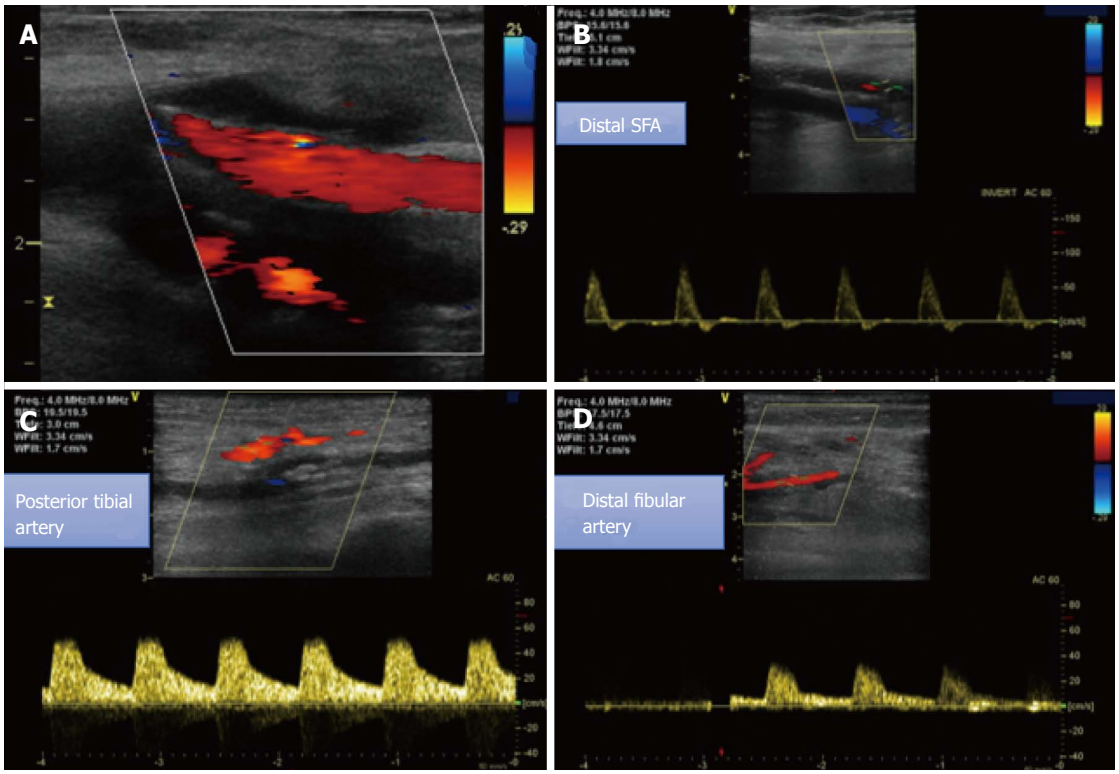

Figure 4 Duplex sonography at follow-up. A, B: Well perfused SFA with biphasic flow in the distal SFA and in the popliteal artery; C, D: Monophasic flow in the distal posterior tibial and fibular arteries. SFA: Superficial femoral artery.

an occluded stent in the mid SFA, facilitating retrograde recanalization. In contrast to most of the reported cases however, the lesion in our patient was more complex, as it did not end in the femoro-popliteal segment, but also involved the proximal and mid part of crural arteries. Thus, due lesion complexity and chronic renal disease, we decided to tackle the lesion in 2 sessions to minimize the risk for contrast induced nephropathy. Indeed, a high amount of contrast agent was necessary within the first recanalization session. Although the final angiographic results after the first session was not optimal due to remaining dissections in the SFA and poor outflow in the crural arteries, vasculature remained open during pharmacologic treatment with aspirin, clopidogrel and fondaparinux for 4 wk. During the second session, further treatment with drug coated balloons was possible, along with recanalization of a crural artery, leading to much better outflow to the foot. This case demonstrates that an "endovascular first" approach may be a valuable and ultimately successful even in very long, complex occlusive lesions, which may further shift treatment from surgical to endovascular treatment procedures in the future.

ARTICLE HIGHLIGHTS

Case characteristics

An 80-year-old female patient with peripheral artery disease (PAD) and long occlusion of the femoro-popliteal artery and below-the-knee arteries after failed bypass surgery, who presented with critical limb ischemia (CLI).

Clinical diagnosis

PAD with CLI (Rutherford Class 5).

Differential diagnosis

Venous ulcer, neuropathic diabetic ulcer.

Laboratory diagnosis

Laboratory markers showed increased inflammation due to the arterial ulcer. In addition, a reduced renal function with an estimated glomerular filtration rate of 36 mL/min per 1.73 m² was noticed.

Imaging diagnosis

PAD was diagnosed by duplex sonography and magnetic resonance angiography (MRA) and was confirmed by digital subtraction angiography (DSA).

Pathological diagnosis

PAD with CLI (Rutherford Class 5).

Treatment

Endovascular strategy using percutaneous balloon angioplasty and without stent placement.

Related reports

The direct stent puncture technique has been used for the recanalization of complex femoro-popliteal occlusive disease in cases were an antegrade recanalization is not successful. The lesion in the patient was more complex, as it did not end in the femoro-popliteal segment, but also involved the proximal and mid part of crural arteries.

Term explanation

CLI is a life-threatening condition due to advanced occlusive PAD, usually

accompanied by ischemic rest pain, arterial ulcers and gangrene. If left untreated this condition will in major amputation, sepsis and death.

Experiences and lessons

In patients with complex femoro-popliteal occlusive disease, the direct stent puncture technique may facilitate recanalization of very long occlusive lesions without the need of bypass surgery. An endovascular first approach needs to be considered in such patients, who usually are bad candidates for surgery due to cardiopulmonary disease and other comorbidities.

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CASE REPORT

Transposition of the great arteries - a phenotype associated with 16p11.2 duplications?

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Author contributions: Lauridsen MH conducted the primary research, selected the patients, obtained informed consent from the parents and children, retrieved the blood samples, and communicated the genetic results to the families; Vestergaard EM performed and interpreted the chromosomal microarray analyses; Karunanithi Z collected the patient information from medical records; Karunanithi Z, Vestergaard EM and Lauridsen MH collectively summarized the data and wrote the manuscript.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Abstract

Genetic analyses of patients with transposition of the great arteries have identified rare copy number variations, suggesting that they may be significant to the aetiology of the disease. This paper reports the identification of a 16p11.2 microduplication, a variation that has yet to be reported in association with transposition of the great arteries. The 16p11.2 microduplication is associated with autism spectrum disorder and developmental delay, but with highly variable phenotypic effects. Autism and attention deficit disorders are observed more frequently in children with congenital heart disease than in the general population. Neonatal surgery is proposed as a risk factor, but as yet unidentified genetic abnormalities should also be taken into account. Thus, congenital heart abnormalities may constitute a part of the phenotypic spectrum associated with duplications at 16p11.2. We suggest chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

Key words: Transposition of the great arteries; Copy number variation; Genetics; 16p11.2; Microduplication

Core tip: Rare copy number variations may be of significance to the aetiology of transposition of the great arteries. This paper reports, for the first time, the finding of a 16p11.2 microduplication in a patient with transposition of the great arteries. Recognizing a possible genetic association to transposition of the great arteries will spur investigations into associated phenotypic effects such as developmental delays, thus allowing for earlier identification and treatment. We recommend that chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

Karunanithi Z, Vestergaard EM, Lauridsen MH. Transposition of the great arteries - a phenotype associated with 16p11.2 duplications? *World J Cardiol* 2017; 9(12): 848-852 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i12/848.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i12.848

INTRODUCTION

Structural gene mutations are emerging as important causes of congenital heart diseases[1]. Transposition of the great arteries is a rare, life-threatening form of congenital heart disease. In contrast to some congenital heart defects, such as atrioventricular septal defects and tetralogy of Fallot, simple transposition of the great arteries is rarely associated with syndromes[2].

Although the aetiology of the disease of is currently unknown, rare copy number variations have recently been identified in patients with transposition of the great arteries[1,3-5] (Table 1). To investigate this further, we screened 13 patients with transposition of the great arteries for copy number variations using high-resolution chromosomal microarray analyses. Approximately half of the screened patients had additional congenital heart diseases.

CASE REPORT

Here, we present the case of a young patient with a genetic mutation that has yet to be reported in association with transposition of the great arteries.

Blood samples were collected from patients and their parents during planned visits. Informed consent to perform chromosomal microarray was obtained. Chromosomal microarray (Agilent Technologies Inc., Santa Clara, CA, United States; 180K CGH for nine patients or 400K CGN + SNP for four patients) was performed on DNA extracted from blood leucocytes as per the manufacturer's protocol.

In one patient, the chromosomal microarray revealed a 0.5 Mb duplication at chromosome 16p11.2 {arr(hg19) 16p11.2 [(29664529-30198600)] × 3 mat} covering the region involved in chromosome 16p11.2 duplication syndrome (OMIM 614671). This microduplication was subsequently detected in the patient's 35-year-old Caucasian mother, who was phenotypically unaffected. The mother was without any cardiac symptoms or murmurs and was not interested in further examinations of her heart.

The patient was born at gestational age 40 wk, weighing 3.06 kg and measuring 50 cm in length. The patient's Apgar score was 9 at one minute and 10 at five minutes. In addition to transposition of the great arteries, a pulmonary valve stenosis and ventricular and atrial septal defects were present. The patient had an arterial switch operation at birth and the Nikaidoh procedure at 7 years of age. Postoperatively, the patient achieved a relatively high level of activity and had no cardiac or respiratory discomfort. At 8 years of age, the patient was diagnosed with attention deficit hyperactive disorder. The patient was followed until the age of 9.5 years.

The 16p11.2 microduplication is associated with autism spectrum disorder and developmental delay, but with highly variable phenotypic effects. This duplication does not always result in severe impairment and may be inherited from a parent with minimal or no clinical features[6]. The 16p11.2 microduplication has not previously been associated with transposition of the great arteries. In the Decipher database, two cases of persistent arterial duct and one case of ventricular septal defect were seen among all patients with a 16p11.2 microduplication[7].

DISCUSSION

Transposition of the great arteries is one of the more severe congenital cardiac defects, but only few studies have investigated the possible aetiology of this defect[1,2]. Two clinical reports have documented a variety of genetic variations associated with transposition of the great arteries[4,5]. On a review of the literature, Unolt *et al*[3] identified frequent syndromes, such as Turner and Noonan, that were rarely associated with transposition of the great arteries; however, a sporadic association with several other genetic variations is possible (Table 1). Costain *et al*[2] studied a cohort of patients with transposition of the great arteries (n = 101) and identified 11 different rare copy number variations, none of which were found in the control group (n = 10528)[2]. Osoegawa *et al*[8] searched for candidate gene loci and sex chromosome aneuploidy among patients with conotruncal cardiac anomalies, of which 194 patients had transposition of the great arteries. They identified a 22q11.22 microdeletion in one patient, an 8p23.2 micro duplication in another patient, and sex chromosome abnormalities (47XYY and

Table 1 Known genetic associations with transposition of the great arteries

		Cytoband	Ref.
Non-syndromic	ZIC3	Xq26.3	Bamford *et al*[12]
	Nodal	10q22.1	Nomura *et al*[13]
	CFC1	2q21.1	Bamford *et al*[12]
	Smad2	18q21.1	Nomura *et al*[13]
		1p31.1	Costain *et al*[2]
		3q25.33-q25.32	Costain *et al*[2]
		4q28.3-4q28.2	Costain *et al*[2]
		7q21.11	Costain *et al*[2]
		8p22	Costain *et al*[2]
		12q24.33	Costain *et al*[2]
		13q13.1-13q13.2	Costain *et al*[2]
		16p12.3-16p13.11	Costain *et al*[2]
		16p12.2	Costain *et al*[2]
		Xp22.12	Costain *et al*[2]
		16p11.2	Current paper
Syndromic	CHARGE		Unolt *et al*[3]
	Deletion 11q		Jacobsen *et al*[14]
	Deletion 18p		Digilio *et al*[15]
	DiGeorge/deletion 22q11		Van Mierop *et al*[16]
	Heterotaxy (right isomerism)		Marino *et al*[17]
	Marfan syndrome		Unolt *et al*[3]
	Noonan syndrome		Unolt *et al*[3]
	Trisomy 18		Unolt *et al*[3]
	Trisomy 8		Unolt *et al*[3]
	Tuberous sclerosis		Jiang *et al*[18]
	Turner syndrome		Unolt *et al*[3]
	VACTERL		Unolt *et al*[3]
	Williams syndrome		Unolt *et al*[3]

47XXY) in two patients with transposition of the great arteries.

We are the first to document the presence of a 16p 11.2 microduplication in a patient with transposition of the great arteries. Deletions and duplications of the recurrent 600 base pair region on chromosome 16p11.2 are frequent findings in patients with autism spectrum disorders and the concomitant finding of congenital heart disease may be an incidental finding not caused by the microduplication[9]. It is, however, well known that congenital abnormalities can occur in the context of recurrent duplications associated with susceptibility to intellectual disability.

Autism and attention deficit disorders are observed more frequently in children with congenital heart disease than in the general population[10]. Neonatal surgery is proposed as a risk factor[11], but as yet unidentified genetic abnormalities should also be taken into account.

Thus, congenital heart abnormalities may constitute a part of the phenotypic spectrum associated with duplications at 16p11.2. We suggest chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

In conclusion, rare copy number variations may be of significance to the aetiology of transposition of the great arteries. This paper reports, for the first time, the finding of a 16p11.2 microduplication in a patient with transposition of the great arteries. Recognizing a possible genetic association to transposition of the great arteries will spur investigations into associated phenotypic effects such as developmental delays, thus allowing for earlier identification and treatment. We therefore recommend that chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

ARTICLE HIGHLIGHTS

Case characteristics

Young patient diagnosed with transposition of the great arteries and a 16p11.2 microduplication.

Clinical diagnosis

The child deteriorated after birth, when the arterial duct closed. Echocardiography revealed transposition of the great arteries, pulmonary valve stenosis and ventricular and atrial septal defects. Around school age the child was diagnosed with attention deficit disorder.

Differential diagnosis

Regarding deterioration after birth, differential diagnoses are: Neonatal sepsis, metabolic disease, and other cyanotic heart defects. Neonatal surgery is a risk factor for attention deficit disorder.

Laboratory diagnosis

Chromosomal microarray revealed the 0.5 Mb chromosomal duplication at chromosome 16p11.2.

Imaging diagnosis

The congenital heart diseases were diagnosed using echocardiography.

Treatment
The transposition of the great arteries was treated with an arterial switch operation at birth and the Nikaidoh procedure at the age of 7 years.

Related reports
Transposition of the great arteries is rarely associated with genetic variations. Transposition of the great arteries have once before been associated with a 16p13.11 duplication (Ref. [19]). The authors are the first to report the 16p11.2 microduplication in association with transposition of the great arteries.

Term explanation
Copy number variation: A structural variation in the DNA that results in the cell having an abnormal number of copies of one or more sections of the DNA.

Experiences and lessons
The case document that copy number variations may be of significance in transposition of the great arteries and chromosomal microarray should be considered part of the diagnostic work-up in these patients.

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LETTERS TO THE EDITOR

Transcatheter aortic valve implantation operators - get involved in imaging!

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Abstract

Pre-procedural planning is the key element of transcatheter aortic valve implantation (TAVI). Multislice computed tomography of the chest, abdomen and pelvis with the ability to perform a 3-dimensional reconstruction has become the cornerstone of pre-procedural planning. We would like to encourage TAVI operators (interventional cardiologist and surgeons) to get involved in imaging. All TAVI operators should know how to assess the annulus, the annular root, and the iliofemoral access. We strongly believe that this will improve outcomes of this evolving procedure.

Key words: Aortic stenosis; Transcatheter aortic valve implantation; Transcatheter aortic valve replacement; Imaging; Computed tomography

Core tip: We have noticed that only a minority of interventional cardiologists and cardiac surgeons routinely look at their patients MDCTs and know how to perform a three dimensional multiplanar reconstruction. With this editorial, we would like to encourage all transcatheter aortic valve implantation (TAVI) operators to get involved in cardiac imaging. We do believe that this will improve outcomes. In case a complication occurs, TAVI operators will be more likely to understand the nature of the complication and learn from it. And this again will lead to improved outcomes in future.

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TO THE EDITOR

Transcatheter aortic valve implantation (TAVI) is now routinely performed in inoperable, high-risk, and

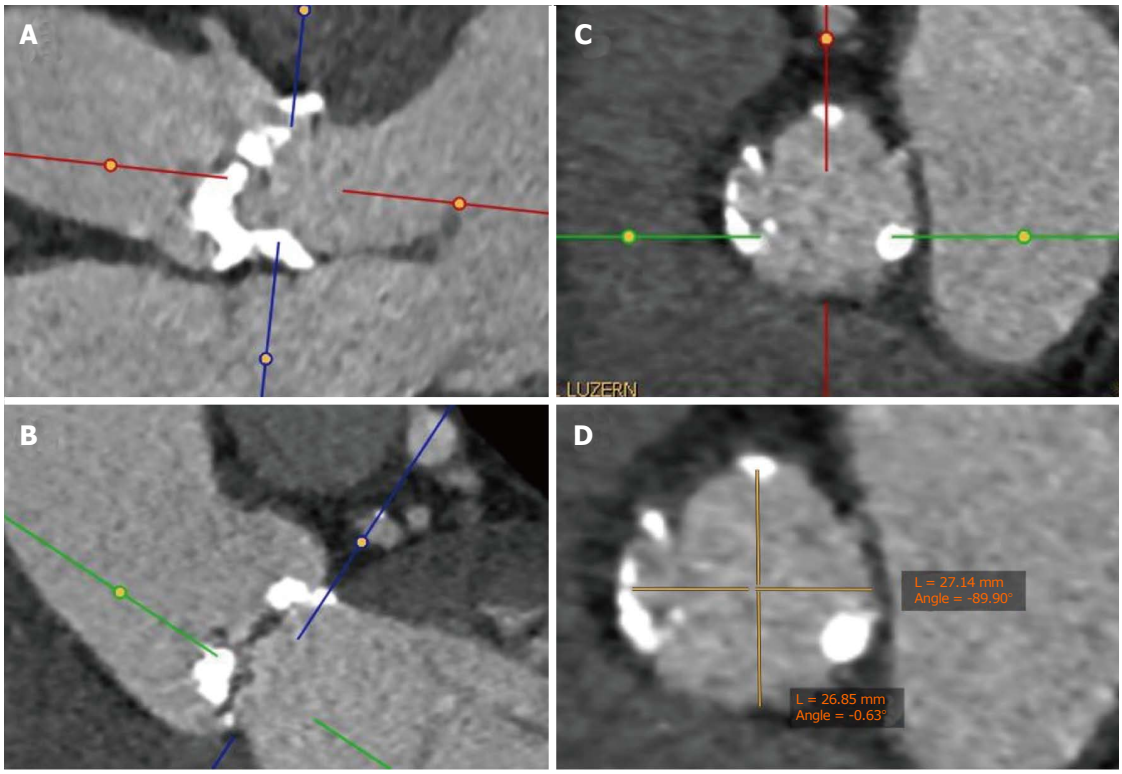

Figure 1 Example of a multiplanar reconstruction of the aortic annulus. A and B: Double-oblique MSCT images at the basal insertion of the calcified native cusps; C: Double-oblique reconstruction at the level of the aortic annulus. The aortic valve leaflets are just barely visible at the level of the ventriculoarterial junction; D: Measurement of the short and long diameter at the level of the aortic annulus. MSCT: Multislice computed tomography.

intermediate risk patients with low mortality- and complication rates[1,2]. Some of the key elements contributing to these impressive results are pre-procedural patient evaluation by the multidisciplinary HeartTeam, and pre-procedural imaging[3,4].

The important role of multislice computed tomography (MSCT). MSCT of the chest, abdomen and pelvis with 3-dimensional reconstruction has become the cornerstone of pre-procedural planning. MSCT is now routinely performed to assess the aortic annulus, the distance between the aortic annulus and the coronary ostia and the suitability for the transfemoral access[3,5]. Nowadays matured post-processing imaging software is widely available to perform these measurements automatically and create standardized reports[6]. However, automatic measurements may not include the degree and distribution of calcification and may not take into account all aspects of the anatomy. Most of the TAVI operators rely on such reports or on numbers and measurements reported by the radiologist[7-9]. Therefore, we would like to encourage all TAVI operators to get involved in imaging and learn how to perform a 3-dimensional multiplanar reconstruction.

Choosing the valve type and size. It has been shown that left ventricular outflow tract (LVOT) calcification is associated with an increased risk for annular rupture during TAVI with balloon-expandable prostheses[10]. Extensive calcifications at the native aortic valve may increase the risk for paravalvular regurgitation or need for a permanent pacemaker[11,12]. As an interventional cardiologist or cardiac surgeon, we can easily perform multiplanar reconstructions of the aortic annulus not only to measure the dimensions of the annulus but also to get an impression of the distribution of calcification of the valve leaflets and the LVOT (Figure 1)[13]. Based on all information including the annular perimeter, area, distribution of calcification and anatomy of the aortic root, valve type and size can be chosen more specifically as part of a patient tailored therapy (Figure 2).

Assessment of the coronary artery height. The "Instructions for use" of different valves include specific recommendations for the minimal coronary artery height. However, the risk for coronary obstruction is greatly increased in patients with bulky atheroma or calcifications at the tip of the leaflets, a smaller sinus of valsalva diameter, narrow sinotubular junction and different patient characteristics like female gender or patients with previous surgical bioprosthesis[14]. Measuring the coronary artery height with MSCT is a great screening tool, but '"virtual implantation" by the operator comparing the length of the leaflets with the distance between annulus and coronary ostia and also assessing the distribution of calcifications may allow much better risk stratification (Figure 3). Radial strength depends largely on the valve type. Whereas the widely used balloon-expandable valves consist of cobalt chromium, self-expanding valves are composed of nitinol thus applying less radial force to the tissue[14]. Accordingly, a self-expandable and retrievable valve might be preferable in patients at risk for coronary obstruction. Moreover, in case of borderline

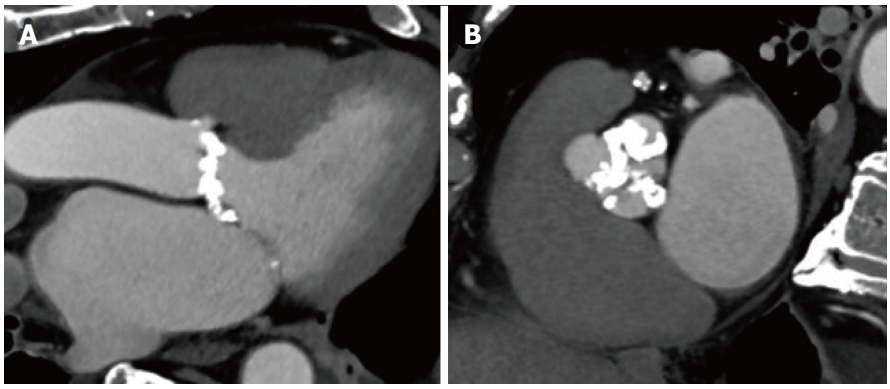

Figure 2 Cardiac multislice computed tomography showing a patient with heavy calcifications extending into the left ventricular outflow tract and a shallow sinus. This anatomy is associated with increased risk for annular rupture in patients undergoing TAVI with a balloon expandable valve. A: Three chamber view of the heart showing a patient with heavy calcification extending from the aortic annulus into the LVOT and a shallow sinus; B: Short axis view of the aortic valve showing heavy calcified aortic leaflets. LVOT: Left ventricular outflow tract; TAVI: Transcatheter aortic valve implantation.

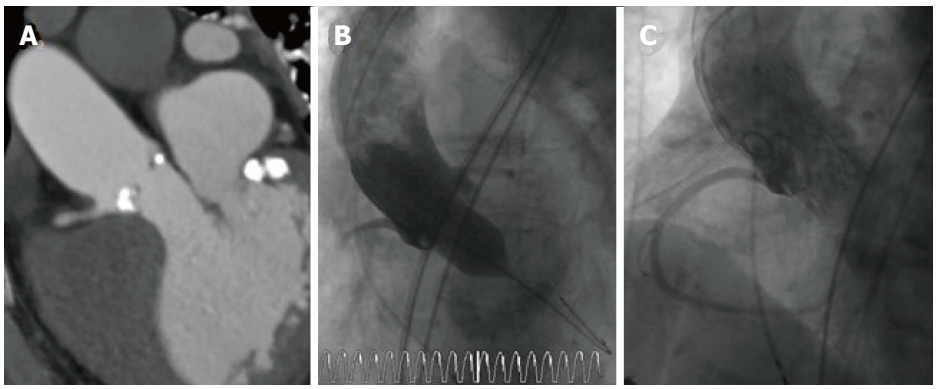

Figure 3 Patient undergoing transfemoral transcatheter aortic valve implantation with a very low ostium of the right coronary artery. A: Patient with a very low ostium of the right coronary artery but potentially a large enough sinus valsalva for TAVI; B: Balloonvalvuloplasty with simultaneous injection of contrast media to estimate the risk for coronary obstruction; C: Successful implantation of an Evolut R. Supraannular injection shows a patent right coronary artery. TAVI: Transcatheter aortic valve implantation.

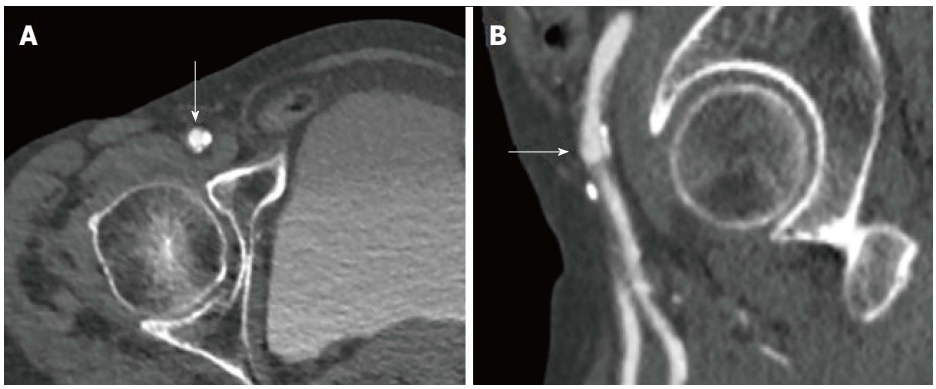

Figure 4 Multislice computed tomography showing calcified right common femoral artery in a patient undergoing transfemoral transcatheter aortic valve implantation. A: Right common femoral artery with an arrow pointing at the ideal puncture site above the calcification; B: Right common femoral artery with an arrow pointing at the ideal puncture site above the height of bifurcation of the common femoral artery in relationship to the femoral head.

anatomy, balloonvalvuloplasty with simultaneous contrast media injection may allow to estimate the risk for coronary obstruction during valve deployment. In patients considered at high risk for coronary obstruction placing a coaxial guiding catheter extension such as the GuideLiner catheter (Cascular Solutions Inc., Minneapolis, MN, United States) in the coronary artery during valve deployment may allow emergent percutaneous coronary intervention.

Choosing the ideal puncture site. Finally MSCT is routinely used to evaluate size, tortuosity and calcifications of the iliofemoral arteries and to determine

the feasibility of transfemoral access[15]. MSCT provides detailed information about the height of the bifurcation of the common femoral artery in relationship to the femoral head. Furthermore, it allows visualization of the inferior epigastric artery which is located within the inguinal ligament. Finally, MSCT shows the extent of calcification at the level of the potential puncture site (Figure 4). Knowing your patients anatomy allows to perform a precise puncture under fluoroscopy guidance thus minimizing the risk for vascular injury[16,17].

How to get involved in imaging, and why? Potential TAVI candidates are discussed by the interdisciplinary HeartTeam consisting of non-invasive cardiologists specialized in cardiac imaging, interventional cardiologists and cardiac surgeon to define the best treatment option for the individual patient. Evaluation of associated comorbidities that may limit the life expectancy or the recovery after the procedure is of particular importance. Results from pre-procedural invasive angiogram, echocardiogram and MSCT are reviewed for each patient. We would like to encourage all TAVI operators to review their patients MSCT again immediately before the procedure. Look at the iliofemoral access to choose the better side with less calcification or tortuosity, and choose the ideal puncture site. Then, perform a three dimensional multiplanar reconstruction of the annulus, measure the annular diameters, perimeter, and the area. Look for calcification at the level of the annulus, but also at the level of the LVOT. Finally, review the root and the coronary arteries. With routine, this can be performed in 2-3 min in most patients. There are two potential advantages of being able to analyze your patient's images. First, you may improve your patient's outcomes. Second, if you have a complication, you are more likely to understand it and learn from it. And this will again lead to better outcomes in the future.

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