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Topological Data Analysis of Coronary Plaques Demonstrates the Natural History of Coronary Atherosclerosis and its Association with Patient Outcome

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Abstract
Aims: We built a patient network based on the similarity of quantitative coronary plaque characteristics from coronary computed tomography angiography (CCTA), to identify distinct groups of patients and its association with coronary plaque progression and outcome.
Methods and results: Patients who underwent two CCTAs at a minimum of 24 months' interval were enrolled (n=1,264). A similarity network of patients was built by topological data analysis based on quantitative coronary plaque analysis of the three coronary arteries on CCTA. Three distinct groups of patients were identified by topological data analysis. Group A had the least amount of coronary plaque (27.3±36.6mm^3) in the entire coronary tree. Group B had a moderate amount of coronary plaque (87.6±133.6mm^3) with relative enrichment of fibrofatty component and necrotic core (31.8±20.2%, 5.2±7.1% of the total plaque, respectively) components. Group C had the largest amount of coronary plaque (255.6±243.3mm^3) and was enriched for dense calcium component (47.9±20.9% of the plaque). At follow-up, total plaque volume, fibrous and dense calcium volumes increased in all groups, but fibrofatty component decreased in group B and C, whereas necrotic core volume decreased in only group B (all p-value<0.05). Group B showed a higher incidence of acute coronary syndrome than other groups (0.0% vs. 1.8% vs. 1.2% for group A, B, C; p-value=0.040) but group C had the highest incidence of revascularization (3.6% vs. 20.3% vs. 23.8% for group A, B, C; p-value<0.001).
Conclusion: Topological data analysis of volumetric coronary plaque composition on CCTA identifies distinct groups of patients with different plaque dynamics and clinical outcomes.
Keywords: coronary; atherosclerosis; topology; progression; outcome.

Introduction

Coronary computed tomography angiography (CCTA) is a useful noninvasive tool commonly used to characterize coronary plaques both qualitatively and quantitatively.(1) Previous studies reported that certain CCTA features of coronary plaques, such as positive remodeling, spotty calcification, napkin ring sign, low attenuation plaque, and substantial plaque burden, are associated with an increased risk of future adverse cardiovascular events. These CCTA features also have independent prognostic value in addition to the clinical factors and the severity of stenosis.(2-6) However, considering that the composition of each coronary plaque is so diverse, conventional qualitative CCTA data analysis might be limited to interpret the true diversity and complexity of the coronary atherosclerosis biology.

Along with advances in the field of data science recently, there are a variety of computational techniques that can be used to assess the complex associations in the data. Topological data analysis (TDA) is a network model that aims to look into the data based on its shape and arrangement and has been recently applied to the medical field.(7-9) Building a network model of patients with similar characteristics may provide a novel and yet, an understandable conception of the complex nature of various cardiovascular diseases.

In this study, we hypothesized that the application of TDA on the quantitative coronary plaque characteristics may provide a new understanding of the complex natural history of coronary atherosclerosis. The objective of this study is to build a patient network based on the

similarity of coronary plaque composition from CCTA with the aim to identify distinct groups of patients and its association with coronary plaque progression and outcome.

Methods

Study Population

The study population was from the PARADIGM (Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging) registry (ClinicalTrials.gov NCT02803411).(10-12) Briefly, the PARADIGM registry is an international, multicenter, prospective observational registry study to evaluate the serial changes in coronary atherosclerosis plaques by CCTA. This registry included a total of 2,252 consecutive patients who underwent serial CCTAs at a minimum interval of 24 months from 13 centers. We excluded 492 patients with inadequate CCTA quality for analysis according to the Society of Cardiovascular Computed Tomography guidelines(13,14) and 496 patients with lack of information about the entire coronary vessel data and the clinical outcome data (**Supplementary Figure 1**). Finally, a total of 1,264 patients were analyzed in this study. The study protocol was approved by the ethics committee at each participating center.

Quantitative and Qualitative Analysis of CCTA

All CCTAs were analyzed in the PARADIGM core laboratory at Severance Hospital, Seoul, Korea, in a blinded fashion. Nine experienced independent readers participated in the CCTA data analysis and performed a quantitative and qualitative assessment of baseline and follow-up CCTAs using semi-automated analysis software (QAngio CT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, the Netherlands).(15) For quantitative analysis, the following parameters were

measured from the entire coronary arteries: vessel length, vessel volume, lumen volume, plaque volume, fibrous component volume, fibrofatty component volume, necrotic core volume, and dense calcium volume. The cutoff values of Housefield unit (HU) used for plaque component measurements were: -30 to 75 HU for necrotic core volume, 76 to 130 HU for fibrofatty volume, 131 to 350 HU for fibrous volume, and >351 for dense calcium volume.(16) The proportion/percentage of each plaque component was calculated by the volume of each plaque component divided by the total plaque volume. For qualitative analysis, high-risk plaque features in CCTA were evaluated, including positive remodeling, spotty calcification, napkin ring sign, and low attenuation plaque.(1) The remodeling index is calculated by the maximal stenosis lesion vessel area divided by the proximal reference vessel area, and positive remodeling is defined as the remodeling index of ≥1.1. Spotty calcification is a small (3mm) and dense (>130HU) plaque component surrounded by noncalcified area. Napkin ring sign is defined as a lesion with a central low attenuation area in contact with the lumen and a ring-like high attenuation area surrounding a central area. Low attenuation plaque is a plaque component with HU≤30. The inter- and intra-observer intraclass correlation for total plaque volume was 0.992 and 0.996 ($p<0.001$), respectively, and ranged between 0.95 and 0.99 for each plaque components.(12)

Definitions of Clinical Outcomes

Clinical outcome data were collected by a dedicated physician at each participating center by outpatient clinic visits or telephone call. The primary clinical outcome in this study was incident acute coronary syndrome (ACS, defined as a composite of acute myocardial infarction or unstable angina). The incidence of any death, cardiac death, any revascularization and any myocardial infarction after baseline CCTA were also recorded. All deaths were considered cardiac unless an undisputed non-cardiac cause was present. All clinical outcomes were defined according to the Academic Research Consortium criteria.(17) The median follow-up duration of the study population was 2,990 (interquartile range 2,275-3,446) days after the initial CCTA.

Topological Data Analysis

Topology is a field of mathematics that studies the shape of the data.(18) Although topology has been traditionally used to study abstract objects using shapes and surfaces, topologists have applied their knowledge to evaluate and to visualize high dimensional and complicated data sets, the method of which has been referred to as TDA.(18) The basic concept of TDA is that we can pattern or shape the complex data set using a geometric approach. Data is processed by multidimensional scaling and compressed to the 2-dimensional chart presented by nodes and edges, called “generalized Reeb graph” (**Take-home figure**). Each node represents a certain group of patients sharing common features and each edge stands for the presence of similarity between the nodes. TDA has been recently applied to the medical field to explore complex

biological processes.(7-9) This study used cloud-based software (version 7.9, Ayasdi, Inc., Menlo Park, CA) for TDA.

To build a patient similarity network in this study, a metric to measure the similarity between each patient and a function, termed lens, to describe the layout of the data was defined. We used normalized correlation metric for the metric and 2-dimensional multidimensional scaling for the lens function. The parameters of the similarity metric, resolution and gain, chosen for the current analysis was 30 and 3.0. A detailed explanation of the TDA is described in the **Supplementary Appendix Online**. In the current study, the quantitative coronary plaque composition data and coronary vessel data from the CCTA analysis, including total vessel length, total vessel volume, total lumen volume, plaque volume, fibrous component volume, fibrofatty component volume, necrotic core volume, and dense calcium volume, was used to calculate the metric. The TDA network map was colored according to the components of the coronary plaque and the patient number per node to assess the specific features according to the location on the map. The red color in the Reeb graph indicates a larger number of patients or a severe degree, the yellow to green color indicates intermediate, and the blue color indicates the minimum number of patients or mild degree. The patient groups were categorized according to the most densely populated parts of the Reeb graph (**Figure 1**). We further checked that the generalized Reeb graph is a persistent connected component of the data, consisting of 4 persistent cycles, corresponding to a 1-dimensional “hole” in the Figure.

Statistical Analysis

The categorical variables are presented as the number (percentages). The continuous variables are presented as the mean±standard deviation. Chi-squared test was used for evaluating non-random associations between categorical variables. Analysis of variance or Kruskal-Wallis test was used for comparison of continuous variables between the groups according to the distributions of variables. The distributions of continuous variables were assessed by the Kolmogorov-Smirnov test. The cumulative incidence of clinical outcomes was calculated using Kaplan-Meier analysis, and the log-rank test was used to compare the group differences. The Bonferroni procedure was used for all post-hoc pairwise comparison. All p-values were 2-sided and a p-value<0.05 was considered statistically significant. The statistical package R, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis.

Results

Baseline Characteristics of the Study Participants

A total of 1,264 patients who underwent serial CCTAs at a minimum interval of 24 months were included in this study (**Supplementary Figure 1**). Baseline clinical and plaque characteristics are presented in **Table 1**. The mean age of the study participants was 60.5±9.4 years, and there were slightly more males (57%). Approximately 60% had hypertension and 25% had diabetes. 5.1% of the study population visited the hospital with typical chest pain. The mean total plaque volume of the entire coronary tree was 117.4±181.3mm^3 and most of the plaque was composed of fibrous (51.6±79.1mm^3) and dense calcium component (42.9±98.0mm^3).

Topological Network of the Patients based on Quantitative CCTA Features

The TDA network, based on the similarity of the quantitative coronary plaque characteristics on CCTA, is shown (**Figure 1**). We colored each node according to the number of patients included in the node. Based on the density of the population in the TDA network, we could classify the study population into three distinct groups. Group A was mainly located in the left lower side of the network, group B in the upper side, and group C in the right lower side of the network. To classify each patient into distinct groups in the TDA network, 47 patients who overlapped between the adjacent groups were excluded from the analysis

of group comparison. Therefore, a total of 1,217 patients were analyzed for group differences.

Patient and Plaque Characteristics according to the Groups on TDA

Clinical characteristics were different between the groups based on TDA (**Table 2**). From group A to C, the age of the patients increased (57.5±9.3 vs. 59.8±9.3 vs. 64.8±8.2 years in group A, B and C, respectively; p-value<0.001). The trends toward the increasing prevalence of comorbidities were also seen from group A to group C, especially for diabetes mellitus, dyslipidemia, previous coronary artery disease, and prior revascularization.

The volume of each plaque components was graded by color across the TDA network (**Figure 2**). The TDA network showed that patients with a large total plaque volume were mostly aggregated on the territory of group C and partly aggregated on the territory of group B, while those with small plaque volume were aggregated on the territory of group A (**Figure 2A**). This distribution was generally concordant with the distribution of fibrous plaque (**Figure 2B**). Most nodes with the substantial amounts of fibrofatty and necrotic core components were aggregated on the upper part of the network within group B territory (**Figure 2C and D**). On the contrary, patients with a large amount of dense calcium were clustered on the right lower part of the network, mainly within group C territory (**Figure 2E**).

The between-group comparison of the quantitative plaque volumes at baseline CCTA showed the same results with those in the TDA network (**Figure 3 and Table 3**). The volumes of the total plaque, fibrous, and dense calcium plaques increased from group A to group C, and the amounts of fibrofatty and necrotic core components were the largest in group B (all p-values<0.001). When the coronary plaque was qualitatively assessed, the high-risk plaque features were the most frequent in group B than in any other groups (66.5% vs. 80.7% vs. 78.4% for group A, B, and C, respectively; p-value<0.001) (**Supplementary Table 1**).

Distinct Coronary Plaque Progression Nature according to the Groups on TDA

Follow-up CCTA showed that total plaque volume significantly increased regardless of the groups (all-p values<0.001). However, the pattern of plaque progression differed by the groups (**Supplementary Figure 2 and Table 3**). In group A, the absolute volumes of all plaque components increased at follow-up. Notably, this group was the only group that showed a significant growth of the necrotic core and the fibrofatty component volume. In group B, while the absolute fibrous component and the dense calcium volume increased, the fibrofatty and necrotic core component volumes were stationary or decreased, leading to decreased proportions of fibrofatty and necrotic core component. In group C, only the dense calcium markedly increased at follow-up while there was a minimal increase of fibrous volume and the proportions of the

fibrofatty and necrotic core component decreased. These findings suggest that the coronary plaque dynamics differ between groups over time.

Distinct Clinical Events according to the Groups on TDA

During a median follow-up of 2,990 days (interquartile range 2,275-3,446 days), the risk of adverse clinical events and its components were distinct between the groups (**Figure 4 and Table 4**). In the primary outcome analysis, 9 patients in group B and 4 in group C experienced the ACS whereas there was no ACS case in group A. Group B showed a higher incidence of ACS than any other group (0.0% vs. 1.8% vs. 1.2% for group A, B, and C; p-value=0.040). In contrast, the cumulative incidence of any revascularization was the highest in group C and the lowest in group A (3.6% vs. 20.3% vs. 23.8% for group A, B, and C; p-value<0.001). Among the 1,217 patients, 18 patients (2.0%) died and 7 (0.8%) of the mortality were from cardiac causes. The cumulative incidence of any death or cardiac death were not different between the groups.

Discussion

Based on our understanding of the complex natural history of coronary atherosclerosis using the CCTA plaque characteristics and TDA, we identified distinct groups of coronary atherosclerosis patients and analyzed their differential association with coronary plaque progression and outcome. The results demonstrated that there were three distinct groups of patients who shared common features of plaque composition. With these different coronary plaque characteristics, the progression pattern of the plaque was distinct, and the related clinical event was also different between the groups. However, the TDA results also demonstrated that the patients were all connected into one network. These results suggest that the various stages of coronary atherosclerosis occurs along the continuum of plaque progression but that the different groups within this network are associated with distinct clinical event profile.

With high spatial resolution and the ability of attenuation-based tissue characterization, CCTA is a useful noninvasive imaging technology that can evaluate coronary plaque qualitatively and quantitatively, the analysis results of which are similar to the pathological studies.(1,19,20) Considering that a complex biological process of inflammation underlies coronary atherosclerosis,(21) the plaque composition identified from CCTA analysis may be diverse and/or dynamic along with the plaque progression. This diversity and dynamicity of coronary atherosclerosis cannot be fully explained by a mere simple quantification of plaque volume or with certain categorical features of coronary plaque; low

attenuation plaque, napkin ring sign, positive remodeling, and spotty calcification to name a few.(1-6) TDA is a network model that aims to explain the complicated processes based on similarity between the data points. The analysis results using TDA has been recently applied to the medical field, giving new insights such as revealing hidden groups or understanding the process of certain disease in a large data.(7-9) The current study used the patient-similarity network based on TDA to interpret the complex relationships of plaque composition between patients. Based on the TDA analysis results, we demonstrated that there was a continuous but heterogeneous process of coronary plaque progression and that there were distinct groups of patients who shared the common features in coronary plaque composition.

From the CCTA data, we can identify and quantify four types of coronary plaque composition as follows: fibrous, fibrofatty, necrotic core, and calcified components,(12,16) the prognostic value of which have been demonstrated.(2-6,22,23) However, none of the previous studies have investigated the coronary plaque composition within each patient in an integrative fashion. We incorporated these plaque composition and the volume data to find that there were 3 distinct groups of patients. Group A had the least amount of coronary plaque in the entire coronary tree. Patients in group A were younger than any other group and could be considered to be at a relatively early stage of coronary atherosclerosis. Patients in group B or group C were in the more progressed stage of atherosclerosis; however, they shared different plaque characteristics. Group B had a moderate amount of coronary plaque but relatively

abundant in fibrofatty and necrotic core components. Group C had the most substantial amount of coronary plaque and was enriched for dense calcium component. In addition to plaque composition, the qualitative features of vulnerable plaques, such as low attenuation plaque, napkin ring sing, positive remodeling, and spotty calcification, were also different across the groups.(1-5) Considering the nature of each feature, these features are bound to follow the specific plaque composition.

Previous studies reported that certain morphological features from CCTA were associated with cardiovascular events.(2-6,22,23) The previous study by Versteylen et al. reported that total plaque volume and non-calcified volume were related to ACS and had additive predictive value over clinical factors.(4) The Rule Out Myocardial Infarction/Ischemia Using Computer-Assisted Tomography (ROMICAT) II trial demonstrated that high-risk features of coronary plaque increased the likelihood of ACS in patients with acute chest pain.(5) Similar to previous studies, the current study demonstrated that the profile of future clinical events was different among the groups with distinct plaque composition. Compared to group A, group B and C had higher rates of cardiovascular events, including ACS and revascularization. However, group B had the highest incidence of ACS, but group C had the highest incidence of any revascularization. These results suggest that the composition of coronary plaque may be associated with specific future cardiovascular events, in addition to the volume of coronary plaque and the presence of high-risk features.(2-4,22,23)

It is challenging to explore the natural course of coronary plaque because the progression of coronary atherosclerosis can span decades, the investigation of which has been done mainly with invasive measures.(24) Importantly, using noninvasive serial CCTA data, this study demonstrated that the dynamicity of coronary plaque over time was variable, according to the groups from the TDA networks. Considering the complex process of coronary atherosclerosis, it may be hard to conclude that there is a consistent natural history of coronary atherosclerosis.(21) However, from the TDA-based patient similarity network model in our study, we can suggest 2 connected pathways of plaque progression, one with a dominancy of non-calcified plaque but with a modest amount of total coronary plaque volume (group B) and another with a dominancy of calcified plaque and the largest amount of total coronary plaque volume (group C). Notably, the two pathways converge into one in the TDA network model and that with the serial CCTA, there is a tendency towards no growth of the necrotic core nor the fibrofatty volume but with only the increase of calcium component in group C. Considering that plaque calcification is a feature of advanced coronary atherosclerosis,(25) the area of group C in TDA networks, in which a large amount of dense calcium was clustered, might be characterized by the most advanced stage of atherosclerosis. In contrast, the only group that showed a growth of the necrotic core or the fibrofatty plaque volume was group A, whereas there was a decreasing trend of these components in the other two groups, suggesting that the growth of high-risk plaque components predominantly occur in the early stages of coronary atherosclerosis.

Overall, our TDA network model suggested that the progression of coronary plaque could proceed from group A to group B and then group C, or from group A directly to group C. This finding was also supported by the results from the follow-up CCTA data in this study but which patients progress through which pathway would need an in-depth study in the future.

Study Limitations

There are a few limitations to be considered in this analysis. First, this study used cross-sectional CCTA data to classify the distinct groups of patients by plaque characteristics and to present the natural history of plaque progression. Therefore, this analysis result in plaque progression should be considered as hypothesis-generating for a further long-term follow-up study. Second, this study did not take into account of the influence of baseline characteristics or medication on plaque progression. Current follow-up CCTA data may not be sufficient to demonstrate which factors are associated with the plaque progression pathway, partially because of the relatively short duration of follow-up in the current study. Lastly, there may be some limitations in evaluating or quantifying the coronary plaque using CCTA compared to intracoronary ultrasound or optical coherence tomography. However, these invasive measurements are only possible in very limited situations, especially for follow-up serial studies. Additionally, previous studies have reported a good correlation between CCTA and these invasive measurements.

Conclusion

The TDA of volumetric coronary plaque composition on CCTA identified distinct groups of patients with different coronary plaque dynamics and patient outcomes. The current study supported the fact that the composition of coronary plaque is helpful to understand the patients with coronary plaque in addition to to the volume of coronary plaque and the presence of high-risk features. In addition, our network model suggests that there are 2 pathways in plaque progression, and thereby, expands our knowledge on coronary plaque behaviors in the future.

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Figure Legends

Figure 1. TDA network using CCTA parameters, with coloration of the number of patients per node.

The patient similarity networks based on the CCTA data is presented as Reeb graph. The red color in the Reeb graph indicates a larger number of patients, the yellow to green color indicates intermediate, and the blue color indicates the smaller number of patients. The patient groups were categorized according to the most densely populated parts of the Reeb graph. Group A was mainly located in the left lower side of the network, group B in the upper side, and group C in the right lower side of the network. CCTA, coronary computed tomography angiography; TDA, topological data analysis.

Figure 2. Plaque composition of each group displayed on TDA.

The volume of each plaque components was graded by color across the TDA network. The entire plaque (**A**), fibrous component (**B**), fibrofatty component (**C**), necrotic core (**D**), and dense calcium (**E**) volumes are depicted in the Reeb graph. The red color indicates severe, the yellow to green color indicates intermediate, and the blue color indicates mild degree. TDA, topological data analysis.

Figure 3. Comparison of plaque composition volumes according to the groups on TDA.

The quantitative assessment of the plaque volumes at baseline CCTA is presented according to the groups on TDA. The entire plaque (**A**),

fibrous component (**B**), fibrofatty component (**C**), necrotic core (**D**), and dense calcium (**E**) volumes are compared between the groups according to the TDA. *, p-value <0.05 for post-hoc pairwise comparison. CCTA, coronary computed tomography angiography; TDA, topological data analysis.

Figure 4. Cumulative incidence of clinical outcomes according to the groups on TDA.

The cumulative incidences of acute coronary syndrome (A) and any revascularization (B) are compared according to the groups from TDA. TDA, topological data analysis.