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Past Myocardial Infarctions and Gender Predict the LVEF Regardless of the Status of Coronary Collaterals: An AI-Informed Research

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Abstract

BACKGROUND: The degree of the development of coronary collaterals is long considered an alternate – that is, a collateral – source of blood supply to an area of the myocardium threatened with vascular ischemia or insufficiency. Hence, the coronary collaterals are beneficial but can also promote harmful (adverse) effects. For instance, the coronary steal effect during the myocardial hyperemia phase and that of restenosis following coronary angioplasty.

AIM: Our study explores the contribution of coronary collaterals – if any exist – while considering other potential predictors, including demographics and medical history, toward the left ventricular (LV) dysfunction measured through the LV ejection fraction (LVEF).

METHODS: Our cross-sectional design study used convenience sampling of 100 patients (n = 100; a male-to-female ratio of 4:1). We conducted frequentist inference statistics using IBM-SPSS version 24 and Microsoft Office Excel 2016 with the analysis ToolPak plugin; we ran parallel neural networks (supervised machine learning (ML)) and a two-step clustering (non-supervised ML) for robust conjoint inference with frequentist statistics.

RESULTS: The past incidents of myocardial infarction (p = 0.036) and gender (p = 0.072) influenced the LVEF; both are significant predictors at a 90% confidence interval. We found that gender and past incidents of MI influenced the LVEF regardless of the status of coronary collaterals. Our study did not yield any positive or significant findings concerning the status of coronary collaterals or the coronary circulation dominance patterns.

CONCLUSION: Regardless of the status of coronary collaterals, we verified that the female gender is protective of the LV function, contrary to the past infarction incidents that predispose to a deteriorated LV function. Our study's innovation relates to its status as the first study from India to explore the coronary collaterals and the ejection fraction while incorporating frequentist statistics and narrow artificial intelligence to infer reliable results.

Introduction

In 1669, Richard Lower of Amsterdam first described the coronary collaterals [1]. Nearly one century later, in 1757, the Swiss Anatomist Albert von Haller was the next to describe them [2]. During the mid-20th century, researchers could resolve controversies regarding the existence or otherwise of these anastomoses by utilizing different imaging techniques in patients with coronary artery diseases; it took even longer till the 1960s to identify and examine these unique vessels in living patients [3,4]. The coronary collateral circulation and its extent are long considered an alternate – that is, a collateral – source of blood supply to an area of the myocardium that is in jeopardy of blood supply deprivation due to ominous cardiovascular accidents [5]. A well-developed collateral blood supply can benefit the infarct by minimizing the ischemic effects; however, a study conducted by Schaper and coworkers (1979) among patients with a more extensive disease confirmed that angiographic identification of collaterals might also signify an unfavorable prognosis [6].

Reimer (1981) gave a clinicopathological description concerning the survival from a sudden episode of coronary occlusion, which could relate to the status of coronary collaterals [7]. Researchers from the 1970s and 1980s could only document the functional importance of coronary collateral flow measurement [8]. It was not until 2003 did notable achievements were recorded in the *in vivo* measurement of collateral flow in patients diagnosed with coronary atherosclerosis [9]. The established role of the precipitating factors for the formation and dislodgement of atherosclerotic plaques and the protective role of well-developed coronary collaterals in determining infarct size is noted [10]. However, well-developed coronary collaterals could also pose some adverse effects; these are still under study

[10]. For example, the possible adverse effects of a well-developed collateral architecture would be the coronary steal effect during the phase of myocardial hyperemia and that of restenosis after coronary angioplasty [11]. The development of restenosis in the presence of well-developed collaterals relates to the competition between the anterograde flow and the collateral flow [12].

Two recent studies have documented that the incidence of cardiovascular events was less in patients with angiographically demonstrated coronary collaterals provided that they were suffering from a chronic stable disease; however, they could not uniformly demonstrate the same advantage in those suffering from a more severe or an acute form of coronary disability [13]. In 2007, Meier and coworkers had a controversy over the beneficial effects of coronary collaterals resulting from the blunt method they used to gauge the collaterals by coronary angiography; limitations of the study included those related to the sample size and the study duration [14]. Meier and colleagues aimed to study a larger population of 845 patients (mean of age=62 ± 11 years) for 10 years using the method of assessing survival – that is, a 10-year survival analysis – after quantitatively obtained recruitable coronary collaterals; they measured the collateral flow index after a 1 min occlusion of the coronary artery by balloon inflation. Further, Konuri *et al*. theorized that the evolution of the cardiac muscles results from a phase transition from smooth muscles due to the altered pressure loads within the vertebrate circulation [15]. Konuri also explained that the coronary vessels developed from a network of capillaries in early embryology and gradually transformed into the branching type of coronary arteries, which goes in parallel with the conversion of the peristaltic movement of the early embryonic heart into an apex-to-base contraction in the mature heart [16].

The present study aims to determine the coronary collaterals' role in influencing the LV ejection fraction (LVEF). We explored other variables, including patients' demographics and medical history; we analyzed potential predictors, including sex, history of previous episodes of myocardial infarction, diabetes mellitus (DM), hypertension (HPT), and dyslipidemia. We conducted data analysis for robust conjoint inference – based on frequentist statistics and machine learning (ML) – to test our hypothesis.

Materials and Methods

The researchers conducted the study following the standard protocol of the ethics and scientific committee at the department of anatomy at the All India Institute of Medical Sciences in Raipur – India. The institute ethics committee at the All India Institute of Medical Sciences (AIIMS, Raipur – Chhattisgarh, India) approved the study per the registration number ECR/714/Inst/CT/2015/RR-18 on the 22nd of September 2018. The researchers obtained informed consent from each study participant.

The researchers measured the LVEF based on echocardiography while exploring the status of coronary arterial dominance and the coronary collaterals through three-dimensional (3D) echocardiography and transthoracic echocardiography, respectively (Vivid E9, GE Healthcare). Researchers conducted data analytics, including frequentist statistics and ML models, using IBM-SPSS version 24 and Microsoft Office Excel 2016 with the analysis ToolPak plugin. Our study is cross-sectional; it deployed a convenience sampling of 100 patients (n = 100, male-to-female ratio of 4:1).

We categorized the age of participants into three groups, including young adults (<40 years of age), middle-aged adults (40–59 years), and senior adults (60 years and older). Further, age did not differ significantly between individuals with normal and dysfunctional LVEF (57.69 vs. 58.33, p = 0.794). We also referred to the categorization of the magnitude of the LV dysfunction into four groups, including standard or normal (LVEF 50–70%), mild dysfunction (40–49%), moderate dysfunction (30–39%), and severe dysfunction (below 30%).

Our neural network deployed a multilayer perceptron neural, a scaled conjugate gradient optimization algorithm, and a default SPSS allocation of the training set and testing set at 70% and 30% of the whole dataset. The neural networks yielded synaptic weights and independent variables importance analysis as an equivalent measure of the effect size in classical statistics. Two-step clustering utilized Schwarz's Bayesian criterion, and the log-likelihood distance measure.

Results

Our study deployed a convenience sampling of 100 patients (n = 100, male-to-female ratio of 4:1). According to descriptive statistics, we calculated the mean, standard error of the mean, skewness, and kurtosis for age (57.79, 0.961, −0.349, and 0.456), and the LVEF (60.26, 1.110, −0.213, and 0.077). Study participants allocated to males (n = 80, 80%) and females (n = 20, 20%), diabetic (n = 56, 56%) and non-diabetic (n = 44, 44%), hypertensive (n = 60, 60%) and non-hypertensive (n = 40, 40%), and participants with (n = 29, 29%) and without dyslipidemia (n = 71, 71%). Further, patients included those with (n = 56, 56%) and without a history of myocardial infarction (n = 44, 44%). Concerning coronary arterial dominance, patients represented four categories; Right coronary artery (RCA) (83%), Left circumflex (LCX) (9%), RCA+ Left coronary artery (5%), and RCA+LCX (3%), while

patients with coronary arterial collaterals accounted for 40% of the study participants.

Data analysis detected extreme values concerning age and LVEF. However, normality testing using the Shapiro–Wilk test confirmed that age (test statistic=0.987, df=100, p = 0.409) and LVEF (0.985, 100, p = 0.308) followed a normal distribution. Hence, we conducted parametric inferential statistics for hypothesis testing. We also carried descriptive statistics for the scale (continuous) variable, LVEF, while stratifying the sample based on the categorical variables (Table 1). Provisionally, LVEF varied based on three variables, including gender, past myocardial infarction incidents, and coronary arterial dominance. Accordingly, we shall test these assumptions using frequentist statistics.

Table 1: Stratification of left ventricular ejection fraction by independent variables and covariates

Independent variable	Mean	SEM
Gender		
Female	64.9550	2.65826
Male	59.0900	1.19008
Total	60.2630	1.10949
DM		
No	60.8864	1.41448
Yes	59.7732	1.64856
Total	60.2630	1.10949
HPT		
No	59.3725	1.68682
Yes	60.8567	1.47435
Total	60.2630	1.10949
Dyslipidemia		
No	60.6225	1.41336
Yes	59.3828	1.65607
Total	60.2630	1.10949
Coronary arterial dominance		
LCX	60.1556	3.89740
RCA	59.9843	1.24805
RCA+LCA	64.2400	2.92790
RCA+LCX	61.6667	6.17342
Total	60.2630	1.10949
Status of collaterals		
No	60.4733	1.64556
Yes	59.9475	1.28952
Total	60.2630	1.10949
History of MI		
No	63.2295	1.70010
Yes	57.9321	1.39882
Total	60.2630	1.10949

†LCX: Left circumflex, LCA: Left coronary artery, RCA: Right coronary artery, DM: Diabetes mellitus, HPT: Hypertension, MI: Myocardial infarction, SEM: Standard error of mean, LVEF: Left ventricular ejection fraction.

According to our pre-study hypothesis, principles of causality of the Bradford Hill criteria, and the preliminary descriptive statistics, we are assuming that the dependent variable (outcome) LVEF is affected by three independent variables (predictors); coronary arterial dominance, the status of collaterals, and history of MI, as well as covariates, including age, gender, DM, HPT, and dyslipidemia. Therefore, LVEF modulates in correspondence with the heart's inherent properties and biomechanical architecture, past incidents of infarction, and other demographic factors. We shall test this hypothesis while attempting to reconcile frequentist statistics with ML (supervised and non-supervised) to explore predictors that significantly affect the LVEF, which might be valuable to prognosticate which individuals can develop LVEF dysfunction in the future when running predictive models based on our analytics.

Using Pearson's bivariate correlations, age did not correlate significantly with LVEF (Pearson's correlation coefficient=0.017, p = 0.869). Pearson's Chi-square of independence and Fisher's exact test did not yield conclusive results concerning the categorical variables' association. Using SPSS, we ran linear modeling as a function of regression analysis to explore the existence of potential significant predictors concerning LVEF and the status of the LV dysfunction. Linear modeling implemented forward stepwise regression (information criterion = 477.345, accuracy = 6.9%). We realize that potentially hundreds of variables interact to manifest the full variance within the outcome LVEF. Thus, our model is simplistic, while more complex models mandate studies with extensive (larger) samples based on high-dimensional and big data using more advanced statistical packages, probably running on more powerful computers. Our regression model trimmed outliers and transformed the age variable to conduct multiple linear regression properly. The model assigned the predictor importance for two variables only, history of MI (coefficient = 4.657, predictor importance = 0.578, p = 0.036) and gender (−4.394, 0.422, and 0.072) (Figure 1); thus, both predictors are significant at an alpha value of 0.10 (90% confidence interval) and can serve as a predictive model to anticipate LV dysfunction. Based on the results from the regression analysis, we shall further explore the existence of significant between-groups differences based on the former two variables (history of MI and gender) and other variables concerning the LVEF, using the independent t-test, univariate analysis of variance (ANOVA), neural networks (supervised ML), and two-step cluster analysis (non-supervised ML).

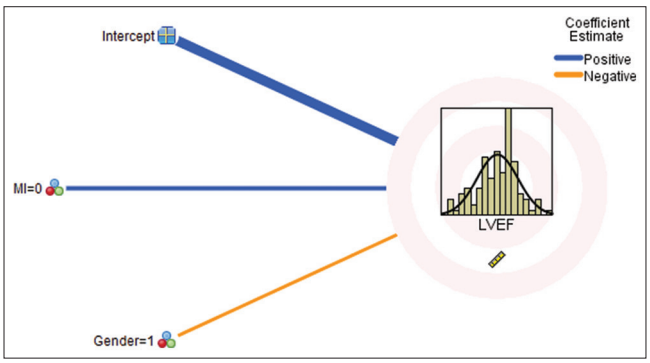

Figure 1: Linear modeling: Summary of the interaction of predictors and outcome. †MI=1 and 0 represent patients with and without a history of MI, respectively. Gender=1 and 2 represent male and female patients, respectively.

Independent t-testing confirmed the existence of significant differences between males and females in connection with LVEF (t =−2.153, df = 98, mean difference =−5.865, p = 0.034) and also based on history of MI (t = 2.428, df = 98, mean difference = 5.297, p = 0.017). There were no statistically significant differences among groups concerning diabetes, HPT, dyslipidemia, or the status of coronary collaterals; these results reconciled with those from the earlier linear regression model. We also evaluated age and coronary arterial dominance as potential predictors of LVEF using one-way ANOVA. Nevertheless, none has a significant

effect on LVEF (age: adjusted R^2 =−0.011, df = 2, mean square = 56.863, F = 0.457, p = 0.635; coronary arterial dominance: adjusted R^2 = −0.024, df=3, mean square = 30.514, F = 0.242, p = 0.867). Further, we ran a summative multifactorial ANOVA by incorporating both variables (age and arterial dominance) to assess the interaction effect that may significantly influence LVEF. However, this model also did not generate any significant predictors (adjusted R^2=-0.017, df = 8, mean square = 99.144, F = 0.792, p = 0.611).

We conducted three neural network analyses; the first deployed the three predictors (coronary arterial dominance, status of collaterals, and history of MI) without covariates; it assigned the highest predictor importance to the history of MI (importance = 0.456, normalized importance = 100%), coronary arterial dominance (0.430, 94.2%), and the status of collaterals (0.114, 25.1%). The second network considered covariates, including age, gender, DM, HPT, and dyslipidemia. Incorporating the covariates conveyed other results while assigning the highest predictors' importance to coronary arterial dominance (Table 2), which mandates running a third summative model. The results of the third network reconciled with the former regression analysis, t-test, ANOVA, and the previous neural networks; it integrated MI history (importance = 0.186, normalized importance = 35.5%), gender (0.290, 55.4%), and age (0.524, 100.0%).

Table 2: The second neural networks model: Independent variable importance analysis

Independent variable	Importance	Normalized importance (%)
Coronary arterial dominance	0.228	100.00
Age	0.211	92.40
Hypertension	0.165	72.20
History of MI	0.112	49.20
Dyslipidemia	0.110	48.50
DM	0.076	33.50
Status of collaterals	0.076	33.20
Gender	0.023	9.90

DM: Diabetes mellitus, MI: Myocardial infarction.

To complement analytics based on artificial intelligence, we ran a non-supervised ML model, using a two-step clustering algorithm by considering two variables: The history of MI and gender. The choice of the independent variables corresponds to the results from the earlier frequentist statistical analysis and the supervised ML models. The clustering model has a good quality (silhouette measure of cohesion and separation = 1). It generated four clusters (size of clusters: 48%, 32%, 12%, and 8%; the ratio of largest to smallest cluster = 6) while assigning the independent variable importance equally to gender (predictor importance = 1) and history of MI (predictor importance = 1). The first and second clusters had males strictly, while the third and fourth clusters had only females. The first cluster has the vast majority of cases with the past incidents of MI; the second cluster has the vast majority of patients without a history of MI; the third cluster has no contribution of cases with a history of MI, while the fourth cluster has a minimal contribution from participants with the past incidents of infarction. In summary, the history of MI and gender influences the LVEF, and it appears that the female gender is protective of the LV function contrary to the past incidents of infarction that predisposes to a deteriorated LV function which corresponds with lower LVEF. Most importantly, our analyses did not show any significant predictor effect of the status of coronary collaterals that might influence the LVEF.

Finally, we conducted a binary logistic regression in which we fed the model with a transformed LVEF scale (continuous) variable into a dichotomous categorical variable (normal versus dysfunctional) as the outcome (dependent) variable, while the model's predictors included all other variables; all were categorical variables, including a transformed age variable. The regression indicated a significant effect – but with an overall weak effect size (Nagelkerke pseudo r-squared = 0.233, exp(B) = 0.176, p < 0.001). Binary logistic regression analysis confirmed somewhat variegated results; it verified a statistically significant effect of two predictors; history of MI (exp(B) = 0.275, p = 0.084) and DM (exp(B) = 0.168, p = 0.035); these were significant at 90% and 95% CI, respectively.

Logistic regression conveyed some novel results concerning significant predictors, specifically DM, which can relate to data reduction by feeding the model with a categorical variable for age rather than a scale measurement and a dichotomous categorical variable (normal versus dysfunctional LV), rather than an ordinal one (normal function, mild dysfunctional, moderate dysfunctional, and severe dysfunctional). We also reinstate that the analytics in this study represent an oversimplification of hundreds of explanatory variables, including cofactors and covariates that interact elaborately and multidirectionally to manifest the complete variance within the observed LVEF.

Discussion

We successfully reconciled frequentist statistics and narrow artificial intelligence models concerning the study objectives; we established potential causal relations between the outcome (LV dysfunction) and the predisposing factors. Predictors included the history of myocardial infarction, DM, gender, and age. Future studies should incorporate a more extensive sample while considering more variables from a high-dimensional dataset.

Hoole *et al*. have noticed the scaffolding effect of coronary collaterals in remodeling the ischemic myocardium [17]. One year earlier (2011), Choi and collaborators demonstrated that well-developed angiographic collaterals distal to the occlusion were associated with a lower frequency and transmurality of the previous infarction; this suggests a protective

role for the demonstrable collaterals distal to the thrombotic occlusion venue [18]. Canto and colleagues (2012) studied the association of age and sex on the presentation of symptomatology; they found a positive correlation with in-hospital mortality among MI patients [19]. Researchers concluded that chronic stable coronary artery disease is a benign disease and to estimate the prognostic significance of the well-developed angiographically documented collaterals, they require the follow-up study of sizable populations of patients [20], [21]. Brugaletta *et al*. have studied the relationship between the presence of collaterals and the incidence of restenosis after coronary angioplasty [22].

The innovative aspects of our study relate to its status as the first observational study conducted in India to explore the coronary collaterals, the ejection fraction, and the LV function based on several risk factors and predictors while incorporating frequentist statistics and ML. The composite of classical statistics and narrow artificial intelligence (nAI) models is novel because it can yield superior results for inferential purposes. Al-Imam introduced the former methodology in a thesis in which he explored pterygomaxillary morphometrics [23,24]. The rationale for a hybrid analytic corresponds to and addresses several elements; for instance, it provides (a) Collateral evidence based on ML algorithms. (b) An alternative method to classical data analytics. (c) Reconciliation of non-Bayesian statistical models, including the univariate and multivariate models, with nAI models. (4) A convergent thinking approach that deals with the research question from alternative standpoints. (5) A novel problem-solving approach. (6) An innovative research method that can serve as a blueprint for future research within the discipline of cardiology, vascular surgery, and precision medicine.

Nonetheless, our research does have limitations other than those inherent to observational studies, including the sample size, which is relatively small. In addition, unique parameters for the sample cannot be fully known, for example, other demographic variables including socioeconomic status and underlying pathologies affecting other body systems. Statistical analyses also possess limitations, for instance, the augmented type-1 (α) statistical error due to multiple data analytics. Besides, the interpretation of causality that we implemented may accept different perspectives, including arguing the basis of the Bradford Hill criteria when classifying specific variables into independent (predictors) and dependent (outcomes) [25].

Future research should explore different populations while accessing representative samples with sufficient participants to detect the hypothesized effect per the pre-study hypotheses. Researchers can conduct more robust study designs of superior level of evidence, including prospective cohorts, quasi-experimental, and experimental designs; the latter include the randomized controlled trials of the supreme level of evidence [26]. Interdisciplinary scholars can deploy our methodology for replicable data analysis within other medical disciplines interlinked with cardiovascular diseases, relevant anatomy, and pathophysiology.

Scholars can explore the adverse effect of psychoactive substances – such as captagon, octodrine, and NBOMe – on the coronary vessels and coronary collaterals while monitoring the adverse effect on the entire cardiovascular system [27-32]. Psychedelics represent a subset of psychoactive and novel psychoactive substances (NPSs), also known as hallucinogens and entheogens, such as LSD, DMT, psilocybin ayahuasca, and cannabis, among others. Psychoactive substances, NPS, and psychedelics can affect the heart and its vasculature, including coronary collaterals and cardiac functioning [33-36]. Researchers can also explore the effect of pathogens – including viral infections – on coronary circulation and its collaterals, for instance, the novel coronavirus 2019 and its variants, responsible for the current SARS-CoV-2 pandemic [37]. These anticipated research attempts – in parallel with the exploitation of big data in medicine – will foster the march from classical medicine toward personalized and precision medicine; Ashley (2016) described precision medicine as “the definition of disease at a higher resolution by genomic and other technologies to enable more precise targeting of disease subgroups, or even individuals, with new therapies. Prominent examples include cystic fibrosis and cancer” [38-40].

Finally, our results indicated that the history of myocardial infarction and gender influenced the LVEF. The female gender is protective of the LV function, contrary to the past incidents of infarction that predispose to a deteriorated LV function and correspond with lower LVEF. Further, the female gender demonstrated a better LV function, irrespective of the past incidents of myocardial infarction. In the present study, we succeeded in reconciling non-Bayesian statistics and techniques of narrow artificial intelligence (ML) to evaluate the ejection fraction of the left ventricle and study its potential predictors – while emphasizing the status of the coronary collaterals. To conclude, our research succeeded in reconciling frequentist statistics and narrow AI models to evaluate the ejection fraction of the left ventricle and study its potential predictors. However, it did not to validate any positive or significant findings concerning the status of coronary collaterals versus the LVEF. Positive and significant findings existed concerning two parameters only: Gender and MI history.

Conclusion

In the present research, we succeeded in reconciling non-Bayesian (frequentist) statistics and narrow AI models to evaluate the ejection fraction of the left ventricle while examining other potential risk factors, including coronary dominance, coronary

collaterals, patients' demographics, and medical history. Nonetheless, our study did not yield any positive or significant findings concerning the status of coronary collaterals versus the LVEF. Positive findings existed concerning two parameters: Gender and history of MI. The history of MI and gender influenced the LVEF; the female gender is protective of the LV function, contrary to the past incidents of infarction that predisposes to a deteriorated LV function and corresponds with lower LVEF. Our results could be of importance for precision and personalized medicine.

Availability of data

The authors abide by an open-access policy concerning medical research data. All data will be available on request from the corresponding author for 3 years following the publication, pending justifiable requests.

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