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Clinical and Echocardiographic Correlates of Plasma Pro-collagen Type III Amino-terminal Peptide Levels in the Community

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Abstract

Background—Left ventricular remodeling is characterized by increased collagen deposition in the extracellular matrix. Levels of plasma pro-collagen type III amino-terminal peptide (PIIINP), a marker of collagen turnover, are elevated in the setting of recent myocardial infarction, heart failure, and cardiomyopathy. Whether plasma PIIINP levels are a useful indicator of subclinical left ventricular abnormalities in ambulatory individuals has not been studied.

Methods—We examined 967 Framingham Heart Study participants (mean age 56 years; 60% women) who underwent routine echocardiography and measurement of plasma PIIINP levels. All participants were free of prior myocardial infarction or heart failure. Multivariable regression analyses were performed to examine the clinical and echocardiographic correlates of PIIINP levels.

Results—Plasma PIIINP levels increased with age and body mass index, but did not significantly correlate with other cardiovascular risk factors including hypertension and diabetes. In multivariable models, there was no association between plasma PIIINP levels and left ventricular mass ($p=0.89$), left ventricular fractional shortening ($p=0.15$), left ventricular end-diastolic dimension ($p=0.51$), or left atrial size ($p=0.68$). Plasma PIIINP levels were positively correlated with tissue inhibitor of metalloproteinase-1 levels (multivariable-adjusted $p=0.001$).

Conclusions—The use of biomarkers of extracellular matrix turnover has generated recent interest, with plasma PIIINP being the most commonly studied biomarker in acute settings. However, our findings in a large, community-based cohort suggest that plasma PIIINP has limited utility for the detection of structural heart disease in ambulatory individuals.

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BACKGROUND

Left ventricular (LV) remodeling plays a critical role in the development of chronic heart failure after hypertension and ischemic heart disease.¹ The processes involved in chronic ventricular remodeling are complex and include changes in both cardiomyocytes and the extracellular matrix. A particularly important finding in the non-cardiomyocyte compartment is interstitial fibrosis, which may lead to deleterious changes in cardiac geometry, ventricular function, and arrhythmogenicity.^{2,3}

One of the hallmarks of interstitial fibrosis is deposition of types I and III fibrillar collagen.⁴ The collagen precursor, pro-collagen, consists of three polypeptide chains arranged in a triple helix, with non-helical N-terminal and C-terminal sequences. The N-terminal and C-terminal peptides are cleaved by endopeptidases after pro-collagen has been secreted from the cell. Elevated levels of pro-collagen type III N-terminal peptide (PIIINP) have been observed in individuals with hypertension,^{5,6} dilated cardiomyopathy,⁷ hypertrophic cardiomyopathy,⁸ and recent myocardial infarction,^{9,10} suggesting that the circulating peptide may be a useful marker of active myocardial collagen synthesis. In a retrospective analysis from the Randomized Aldactone Evaluation Study, high baseline levels of circulating PIIINP were predictive of death and hospitalization in heart failure patients.¹¹ Interestingly, the benefit of spironolactone, a putative anti-fibrotic agent, was observed primarily in participants with plasma PIIINP levels above the median.

Whereas PIIINP has emerged as a promising biomarker for monitoring ventricular fibrosis,¹² studies of plasma PIIINP levels have largely been restricted to hospitalized patients or randomized trial cohorts. The majority of these studies have involved fewer than 200 participants. Little is known about the distribution and correlates of plasma PIIINP levels in larger, ambulatory populations. Similarly, there are few data on the association of plasma PIIINP levels with LV structure and function in individuals without heart failure. Such information may provide insight into the potential role of this marker in assessing the burden of myocardial fibrosis in broader populations. Accordingly, we measured plasma PIIINP levels in nearly 1000 participants drawn from a well-characterized, community-based cohort in which echocardiography was routinely performed. We hypothesized that higher plasma PIIINP levels would be associated with increased LV wall thickness, mass, and chamber dimensions.

METHODS

Study Sample

The Framingham Offspring Study was initiated in 1971 with the enrollment of 5124 offspring (and their spouses) of the original Framingham Heart Study participants.¹³ The Framingham Omni Study was begun in 1994 and included Framingham residents who identified themselves as members of a minority group. Participants were eligible for the present investigation if they attended the sixth examination of the offspring cohort (1995–1998; n=3532) or the first examination of the Omni cohort (1994–1996; n=506 [36% African-American, 40% Hispanic]).¹⁴

To maximize statistical efficiency, we included in the study sample all participants meeting one of the following criteria: echocardiographic end-diastolic LV internal diameter (LVEDD) and wall thickness (LVWT) below their respective sex-specific medians (n=724); LVEDD equal to or exceeding the sex-specific 90th percentile (n=244); LVWT equal to or exceeding the sex-specific 90th percentile (n=244); or both LVEDD and LVWT exceeding the sex-specific 90th percentiles (n=32). Of these 1244 participants (including 200 from the Omni cohort), 1090 (88%) had measurement of PIIINP levels.

A total of 123 additional participants were excluded for the following reasons: history of heart failure or myocardial infarction (n=46), serum creatinine >2 mg/dl or missing (n=24), and other missing covariate data (n=53). We excluded those with renal insufficiency because higher PIIINP levels have been reported in individuals with renal fibrosis, although renal function itself does not appear to affect the clearance of PIIINP.¹⁵ After these exclusions, 967 participants remained eligible (referent group n=592; increased LVEDD group, n=199; increased LVWT group n=196; 20 subjects had both increased LVEDD and increased LVWT).

The study was approved by the Institutional Review Board of Boston Medical Center and subjects gave written informed consent.

Clinical Examination

Participants underwent a history and physical examination that included two blood pressure measurements, laboratory testing, and electrocardiography.¹³ Diabetes and hypertension were defined using contemporary criteria.^{16,17} Cardiovascular disease included ischemic heart disease, heart failure, cerebrovascular disease, or peripheral vascular disease.¹⁸

Laboratory Measurements

Fasting participants underwent phlebotomy in a supine position. Plasma was separated and frozen at -70°C . Plasma PIIINP was measured using a radioimmunoassay (Amersham Pharmacia Biotech). All specimens were processed in duplicate; the mean intra-assay coefficient of variation was 6%. Plasma levels of tissue inhibitor of metalloproteinase-1 (TIMP-1), a marker of collagen synthesis, and B-type natriuretic peptide (BNP), a neurohormonal marker, were measured as previously described.^{19,20}

Echocardiography

All participants underwent two-dimensional and M-mode echocardiography during the clinic visit, using a standard protocol.²¹ Interventricular septal thickness (IVS), posterior LV wall thickness (PW), and LVEDD were measured at end-diastole. Left atrial diameter and LV end-systolic diameter (LVESD) were measured at end-systole. LVWT was calculated as the sum of IVS and PW, and LV relative wall thickness was calculated as LVWT/LVEDD . We estimated LV mass (LVM) using the formula $0.8[1.04(\text{IVS} + \text{LVEDD} + \text{PW})^3 - (\text{LVEDD})^3] + 0.6\text{g}$.²² LV fractional shortening (LVFS) was calculated as $(\text{LVEDD} - \text{LVESD})/\text{LVEDD}$. Valve disease was defined as at least moderate regurgitation or stenosis of the aortic or mitral valve. Reproducibility of echocardiographic measurements was high, as previously reported.²³

Statistical Analyses

Natural logarithmic transformation was performed on variables with highly skewed distributions (PIIINP, LVM, LVWT, relative wall thickness, LVEDD, left atrial diameter, and alcoholic drinks/week).

Clinical correlates of plasma PIIINP levels were studied in the subsample (n=905) of participants without overt cardiovascular disease, using stepwise multiple linear regression models. Clinical covariates included age, sex, ethnicity, body mass index (BMI), smoking, alcohol intake, diabetes, total/HDL-cholesterol ratio, systolic blood pressure, antihypertensive treatment, and heart rate. Self-reported ethnicity was recoded to Caucasian/non-Caucasian. Variables with $p < 0.10$ were retained in stepwise models. We also examined whether plasma PIIINP levels were associated with levels of TIMP-1 and BNP, after adjustment for clinical covariates.

Subsequent analyses used the entire study sample (n=967). Multivariable logistic regression models were used to investigate the relations of log PIIINP with increased LVEDD or increased LVWT.²⁴ Participants with both increased LVEDD and increased LVWT were included in both models. We fitted age-, sex-, height-adjusted models, as well as multivariable models adjusting for these variables plus weight, ethnicity, smoking, alcohol intake, diabetes, total/HDL-cholesterol ratio, systolic blood pressure, antihypertensive treatment, valve disease, and heart rate.

We then fitted multivariable linear regression models to examine the association between plasma PIIINP levels and each echocardiographic variable. Plasma PIIINP was examined as a continuous variable and as categorical variables (sex-specific quartiles) in separate models. Models were adjusted for clinical covariates as above. When applicable, least squares means were transformed back to original units.

Analyses were performed using SAS 8.0 (SAS, Inc., Cary, N.C.). Two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of participants are shown in Table 1. Mean plasma PIIINP was 3.99 ± 4.18 ng/ml. Clinical correlates of plasma PIIINP in participants without overt cardiovascular disease are shown in Table 2. Log PIIINP levels were correlated positively with age ($p=0.03$), hypertension therapy ($p=0.002$), hypertension ($p=0.009$), diabetes ($p=0.03$), and BMI ($p=0.001$). Variables retained in the stepwise multivariable model were age ($p=0.02$), non-white ethnicity ($p=0.09$), and BMI ($p=0.002$), each of which was associated with higher log PIIINP levels.

In logistic regression analyses, although there was a borderline-significant association between log PIIINP levels and increased LVDD after adjustment for age, sex, and height ($p=0.08$), this association was not significant after adjustment for conventional cardiovascular risk factors ($p=0.48$). There was no significant association between log PIIINP levels and increased LVWT in either age-, sex-, and height-adjusted ($p=0.86$) or fully-adjusted logistic analyses ($p=0.23$).

Table 3 shows the association of plasma PIIINP levels with echocardiographic measures. Log PIIINP levels had borderline-significant associations with LV mass ($p=0.07$) and left atrial size ($p=0.06$) in age-, sex-, and height-adjusted models, but not in multivariable-adjusted models. Log PIIINP levels were not significantly associated with other echocardiographic measures. In models categorizing PIIINP levels by quartile, adjusted mean left atrial size increased across quartiles of PIIINP after adjustment for age, sex, and height ($p=0.002$), but not after further adjustment for BMI ($p=0.46$), or BMI and other cardiovascular risk factors ($p=0.48$).

In additional multivariable-adjusted analyses, log PIIINP levels were positively associated with log TIMP-1 ($\beta=0.42$, $p=0.001$) and log BNP ($\beta=0.07$, $p=0.003$).

Statistical Power

We performed post-hoc power analyses to determine whether we had adequate statistical power to detect an association between plasma PIIINP levels and echocardiographic measures in this sample. We calculated that we had 80% power to detect an association between PIIINP and continuous echocardiographic variables if the true partial correlation was 0.09, after adjustment for covariates. For discrete variables (increased LVDD, increased

LVWT), we had 80% power to detect an adjusted odds ratio of 1.37 per SD increment in log PIIINP.

DISCUSSION

Principal Findings

Plasma PIIINP is considered a potential non-invasive marker of extracellular matrix remodeling in the heart.^{5,7,25–27} Prior studies have documented elevated PIIINP levels in patients with a variety of abnormalities influencing cardiac structure or function.^{7,8} In an adequately ‘powered’ study of a community-based sample, we found that plasma PIIINP levels were correlated with age and BMI, but not with LV structure or function after adjustment for conventional risk factors. These findings suggest limited utility for measurement of plasma PIIINP levels to detect subclinical cardiac disease in the ambulatory setting. The validity of our results is supported by the large sample size and the consistency of our findings in both univariable and multivariable analyses. To our knowledge, the present study is the largest investigation of plasma PIIINP levels in humans and the first to focus exclusively on community-based individuals.

PIIINP and BMI

BMI was the most significant correlate of PIIINP levels in this cohort, a finding that extends observations from several smaller studies.^{28,29} Rasmussen and colleagues reported an association between PIIINP levels and both body weight ($r=0.37$, $p=0.004$) and waist circumference ($r=0.35$, $p=0.007$) in a hospital-based study. Interestingly, they found that PIIINP levels decreased during weight loss, and the magnitude of change in PIIINP was correlated with the amount of weight loss.²⁹ A positive correlation between BMI and PIIINP has also been reported in a study of patients attending a rheumatology clinic.²⁸

The origin of elevated PIIINP levels in obese individuals is unknown, as collagen synthesis in a variety of organs may contribute to circulating PIIINP levels.^{30–32} Nonetheless, experimental studies raise the intriguing possibility that elevated PIIINP levels in obesity derive at least partly from the heart. For instance, Carroll and Tyagi observed that rabbits fed 12 weeks of a high fat diet had higher cardiac type III collagen than lean rabbits fed a normal diet.³³ Increased cardiac type III collagen deposition has also been described in the obese Zucker rat model.³⁴ Although the underlying mechanisms for increased cardiac collagen deposition in obesity are unclear, it is tempting to speculate that excessive collagen deposition contributes to obesity-related LV hypertrophy.³⁵ Interestingly, a recent study of obese individuals found that PIIINP levels were independently correlated with indices of insulin resistance, which has also been postulated to play a role in the development of LV hypertrophy.³⁶

We found a positive association between PIIINP levels and hypertension, but this association was not significant after accounting for the effects of age and BMI. Diez and colleagues reported higher levels of PIIINP in 50 individuals with essential hypertension compared with 30 controls, but that study did not adjust for baseline differences in age or BMI.⁵

PIIINP and Echocardiographic Findings

We found marginal age- and sex-adjusted associations of PIIINP levels with LV mass and left atrial diameter, perhaps consistent with the premise that circulating PIIINP levels reflect active collagen synthesis, as would be observed with LV remodeling or left atrial dilation. These associations were attenuated after adjustment for BMI and other cardiovascular risk factors. One interpretation of these findings is that risk factors (including adiposity),

collagen synthesis, and the development of cardiac structural abnormalities belong to the same or overlapping causal pathways.

Several other factors may explain the weak association between PIIINP and echocardiographic abnormalities. First, the presence of extra-cardiac sites of type III collagen production may reduce the specificity of plasma PIIINP levels for LV remodeling. Elevated PIIINP levels have been documented in rheumatologic disorders,^{30,31} liver disease,³² and pulmonary fibrotic diseases.³⁷ Second, most prior studies of circulating PIIINP levels have been conducted in patients with severe cardiac disease, such as recent myocardial infarction^{9,10,26} or congestive heart failure.^{11,38,39} Interstitial collagen deposition may be substantially higher in patients with severe illness, in whom active matrix turnover may be more pronounced, than in clinically stable ambulatory individuals. Nonetheless, it is interesting to note that substantial overlap exists between the range of plasma PIIINP levels found in prior studies and in our study. In a study of 74 patients with acute myocardial infarction, median PIIINP levels ranged between 3 and 4 ng/ml during the first 5 days of admission.⁹ Patients with systolic heart failure randomised in the RALES trial had median PIIINP levels of 3.85 ng/ml.¹¹ In our cohort, median PIIINP levels were 3.0 ng/ml in the referent group, 3.26 ng/ml in those with increased LVID, and 3.33 pg/ml in those with increased LVWT. These data suggest that plasma PIIINP may not offer sufficient discrimination to be clinically useful for distinguishing individuals with and without prevalent cardiovascular disease.

Lastly, smaller studies may be more susceptible to selection bias. Patients and controls in these studies may be sampled from different populations, introducing the possibility that underlying differences in the source populations may contribute to the variation in plasma PIIINP levels. A strength of the present study is that all individuals were drawn from an epidemiologic cohort that has been followed for more than three decades.

Comparison with Other Extracellular Matrix Markers

Prior studies have examined other markers of extracellular matrix remodeling.^{5,19,40} Diez et al. showed that levels of type I carboxy-terminal pro-collagen peptide were associated with LV mass in hypertensive individuals, whereas plasma PIIINP was not.⁵ Type I collagen is more abundant in the extracellular matrix than type III collagen,⁴ although an increase in the proportion of type III collagen may be an early response to pressure overload.⁴¹ Like type III collagen, type I collagen is found in non-cardiac tissue.

We have previously reported age-adjusted associations of LV indices with plasma levels of matrix metalloproteinase-9 (MMP-9) in men⁴⁰ and TIMP-1 in both sexes.¹⁹ The association of MMP-9 with echocardiographic features persists even after adjustment for baseline cardiovascular disease risk factors. MMP-9 and TIMP-1 are involved in the breakdown and accumulation of extracellular matrix collagen. Because these enzymes act proximally in the pathways responsible for extracellular matrix turnover, it is possible that they are more sensitive markers of matrix remodeling than the collagen pro-peptides in pre-clinical individuals. Plasma TIMP-1 levels were significantly correlated with plasma PIIINP levels, even after multivariable adjustment, an observation that may be attributable to the association of both markers with collagen synthesis.

Interestingly, plasma PIIINP was also correlated with BNP levels in multivariable analyses. Because BNP levels are generally low in ambulatory individuals without heart disease,²⁰ our findings suggest that even subtle increases in LV wall stress could result in increased collagen synthesis. A significant relation between plasma PIIINP and BNP has been previously described in patients following acute myocardial infarction.⁴²

Study Limitations

Measurement of plasma PIIINP at a single time point might have led us to underestimate the association between PIIINP levels and echocardiographic indices. Little is known about intra-individual variability in PIIINP levels. Likewise, data from a single occasion do not provide information regarding the progression of LV hypertrophy or dilation. We did not measure other markers of collagen synthesis (type I carboxy-terminal pro-collagen peptide) or degradation (type I collagen carboxy-terminal telopeptide) that may have been related to echocardiographic measures.^{43,44} Additionally, we did not assess genetic factors, which may have explained some of the variation in PIIINP levels. Lastly, transmitral and tissue Doppler measurements were not available at this examination. It is possible that diastolic dysfunction could have been present in some participants otherwise lacking LV structural abnormalities.^{45,46}

Conclusion

There is growing recognition that abnormalities of the heart's non-cardiomyocyte compartment (the extracellular matrix) play a fundamental role in the development of chronic congestive heart failure. Early detection of these abnormalities may allow intervention prior to the development of overt heart failure. While interstitial fibrosis can be demonstrated on endomyocardial biopsy specimens,^{2,3} a non-invasive approach would be necessary to screen asymptomatic individuals. The use of biomarkers of extracellular matrix turnover has generated particular interest, with plasma PIIINP being the most commonly studied biomarker in acute settings.^{7,9,11,39} However, in this large, community-based study, plasma PIIINP levels were not associated with subclinical LV abnormalities after accounting for conventional cardiovascular risk factors. While it is possible that individuals with elevated PIIINP levels developed echocardiographic abnormalities subsequent to the baseline examination, the lack of a cross-sectional association suggests that plasma PIIINP is not a good marker of subclinical structural heart disease.

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Table 1

Clinical Characteristics

	Whole sample (n=967)	According to LV features		
		Referent group (n=592)	Increased LVEDD (n=199)	Increased LVWVT (n=196)
Clinical Data				
Age, years	56±10	54±9	57±10	63±10
Women, %	60	58	63	60
Non-Caucasian, %	12	12	13	11
BMI, kg/m ²	26.8±4.9	25.1±3.7	29.6±6.1	29.9±5.0
Smoking, %	14	15	11	16
Diabetes, %	9	5	13	19
Total/HDL ratio	4.2±1.4	4.1±1.4	4.2±1.3	4.7±1.3
SBP, mmHg	125±20	120±17	130±20	139±22
HTN therapy, %	22	11	28	49
HTN, %	32	19	45	64
Heart rate, bpm	63±10	63±9	62±10	64±10
Drinks/wk	3.5±5.1	3.6±5.0	3.6±5.3	3.4±5.4
Atrial fibrillation, %	1	0	2	3
Valve disease, %	4	1	11	8
Previous CVD, %	6	3	9	13
Plasma PIIINP levels				
Mean, ng/ml	3.99	4.00	4.28	3.73
Median, ng/ml	3.10	3.00	3.26	3.33
Range	0.02–53.26	0.02–43.23	0.54–53.26	0.02–53.26
Echocardiographic Data				
Mean LV mass, g				
Pooled sex	157.3±53.2	125.8±25.5	207.0±45.7	212.4±51.5
Men	186.8±55.6	150.2±17.7	249.3±39.6	254.6±46.3
Women	137.3±40.8	108.4±12.8	182.5±27.5	184.6±32.4
Mean LVWVT, cm				
Pooled sex	1.88±0.31	1.72±0.14	1.91±0.22	2.37±0.25

	Whole sample (n=967)	According to LV features		
		Referent group (n=592)	Increased LVEDD (n=199)	Increased LVWT (n=196)
Men	1.99±0.31	1.83±0.10	2.01±0.22	2.53±0.22
Women	1.80±0.28	1.64±0.10	1.85±0.20	2.26±0.21
Mean LVEDD, cm				
Pooled sex	4.68±0.56	4.43±0.34	5.48±0.38	4.67±0.52
Men	4.97±0.54	4.72±0.26	5.90±0.27	4.96±0.48
Women	4.48±0.48	4.23±0.22	5.24±0.16	4.48±0.45
Mean LVFS, %				
Pooled sex	0.37±0.06	0.38±0.05	0.35±0.06	0.39±0.06
Men	0.36±0.06	0.37±0.05	0.3±0.07	0.38±0.06
Women	0.38±0.05	0.39±0.05	0.36±0.05	0.39±0.06

Values are mean±SD, or percentages. Twenty participants had both increased LVEDD and increased LVWT. HTN, hypertension; total/HDL ratio, ratio of total to high density lipoprotein cholesterol; CVD, cardiovascular disease; SBP, systolic blood pressure.

Table 2

Correlates of Plasma PIIINP in Participants Without Cardiovascular Disease

	Individually		Stepwise Multivariable	
	r	p-value	β -coefficient	p-value
Age	0.07	0.03	0.043	0.02
Female	-0.055	0.10	--	--
Hypertension therapy	0.105	0.002	--	--
Diabetes	0.071	0.03	--	--
Current smoking	-0.064	0.053	--	--
Total/HDL ratio	0.038	0.25	--	--
BMI	0.109	0.001	0.059	0.002
Heart rate	-0.002	0.96	--	--
White	-0.019	0.56	-0.097	0.09
Drinks/wk	-0.042	0.21	--	--
Systolic BP	0.024	0.46	--	--
Hypertension	0.086	0.009	--	--
Valve disease	0.057	0.09	--	--

Plasma PIIINP levels and drinks/week were natural log-transformed. Continuous variables were standardized, SD=1.

Table 3

Relations of Plasma PIIINP to Echocardiographic Indices

	Continuous ln (PIINP)		Sex-specific PIIINP Quartile			
	β^*	p-value	Q1	Q2	Q3	Q4 P (trend)
A. Age-, sex-, and height-adjusted						
LVMI, g	0.027	0.07	157	150	163	159 0.09
LVWT, cm	0.008	0.29	1.87	1.85	1.88	1.90 0.11
LV RWT, %	-0.001	0.92	0.40	0.41	0.40	0.41 0.40
LVEDD, cm	0.009	0.11	4.68	4.60	4.76	4.66 0.39
LVFS, %	-0.005	0.11	0.38	0.38	0.37	0.37 0.27
LA, cm	0.014	0.06	3.82	3.86	4.00	3.91 0.002
B. Multivariable-adjusted						
LVMI, g	0.002	0.89	161	154	157	156 0.21
LVWT, cm	-0.003	0.62	1.89	1.87	1.86	1.87 0.32
LV RWT, %	-0.007	0.45	0.41	0.41	0.40	0.41 0.81
LVEDD, cm	0.004	0.51	4.71	4.63	4.72	4.65 0.41
LVFS, %	-0.005	0.15	0.37	0.38	0.37	0.37 0.51
LA, cm	0.003	0.68	3.86	3.91	3.95	3.88 0.48

Continuous variables are log-transformed.

* Regression coefficient associated with log PIIINP, from models with the echocardiographic measure as the dependent variable. For columns with the PIIINP quartiles, least squares means are presented, adjusted for age, sex and height in the upper panel (Model A) and age, sex, ethnicity, height, weight, smoking, alcohol intake, diabetes, total/HDL-cholesterol ratio, systolic blood pressure, antihypertensive treatment, valve disease, and heart rate in the lower panel (Model B).