Effect of Recruitment of Acute Coronary Collaterals on In-Hospital Mortality and on Left Ventricular Function in Patients Presenting With ST Elevation Myocardial Infarction

Usaid K. Allahwala, MBBS, Bsc(Med)Hons[a,b,*], James C. Weaver, MBBS, PhD[c,d], Gregory I. Nelson, MBBS[a], Daniel Nour, MBBS[a], Max Ray, MBBS[a], Jonathan L. Ciofani, MBBS[a], Michael Ward, MBBS, PhD[a], Gemma Figtree, MBBS, PhD[a,b], Peter Hansen, MBBS, PhD[a], and Ravinay Bhindi, MBBS, PhD[a,b]

Recruitment of the coronary collateral circulation is frequently observed during ST elevation myocardial infarction (STEMI) and is of uncertain significance. The aim of this study was to identify and determine the predictors and prognostic implications of the presence of robust collaterals during STEMI. All patients presenting to a large tertiary centre with a STEMI undergoing percutaneous coronary intervention from 2010 to 2018 were reviewed. Patients with poor collateral recruitment were defined as those with Rentrop grade 0 or 1 collaterals, whilst patients with robust collateral recruitment were defined as Rentrop grade 2 or 3. A total of 1,625 patients were included in the study, with 1,280 (78.8%) patients having poor collateral recruitment and 345 patients (21.2%) having robust collateral recruitment. Patients with robust collaterals were younger (63.1 vs 65.1 years, $p < 0.05$), had a longer ischemic time (628.5 minutes vs 433.1 minutes, $p < 0.0001$), and more likely to have a chronic total occlusion of a noninfarct related artery (10.4% vs 5.3%, $p < 0.001$). The presence of robust collaterals was associated with higher rates of normal or mildly impaired left ventricular function (83.5% vs 63.2%, $p < 0.0001$) and lower in-hospital mortality (2.1% vs 7.6%, $p < 0.0001$). After correcting for left ventricular function, collateral recruitment was not an independent predictor of mortality. In conclusion, in patients presenting with STEMI, the presence of robust coronary collaterals appears to be associated with improved left ventricular function. Further research is required to identify mechanisms of collateral maturation and recruitment. **(Am J Cardiol 2020;125:1455−1460)**

The coronary collateral circulation is a network of preformed anastomotic channels which connect the territory supplied by one epicardial coronary artery with that supplied by another.[1] Naturally occurring coronary collaterals appear in all species, with significant variation in their extent and development.[2] These collateral arteries therefore provide an alternative source of blood supply to myocardium that has been jeopardized by occlusive coronary artery disease, as is seen in the setting of a ST elevation myocardial infarction (STEMI). Consequently, the presence of collaterals may help to preserve myocardial function and improve clinical outcomes.[3] Coronary collaterals are rapidly recruited, often observed during coronary angiography for primary percutaneous coronary intervention (pPCI), and whilst some[4,5] observational studies have shown a prognostic benefit with collaterals, not all have agreed.[6] We sought to determine the prevalence, predictors and impact of the presence of collaterals, recruited acutely during a STEMI on clinical outcomes.

Methods

We reviewed patients presenting to our tertiary centre with a diagnosis of STEMI, undergoing pPCI or rescue PCI for unsuccessful thrombolysis, from July 2010 until December 2018. All patients had pretreatment with aspirin, unless they were unable to tolerate per oral medications. Therapeutic intra-arterial heparin was administered at the beginning of the procedure, whilst intracoronary nitrates prior to intervention was not routinely administered, due to the emergent nature of the procedure. Glycoprotein IIb/IIIa inhibitor use was left to operator discretion.

Patients who had had a prior coronary artery bypass graft, or spontaneous coronary artery dissection were excluded. Electronic medical records were reviewed to identify procedural characteristics, presence of preinfarct angina, in-hospital course, left ventricular (LV) function, and biochemical results. LV function was assessed by transthoracic echocardiogram following STEMI, or if not performed, then based on ventriculography at the time of the procedure. Invasive hemodynamics

[a]Department of Cardiology, Royal North Shore Hospital, Sydney, Australia; [b]The University of Sydney, Sydney, Australia; [c]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia; and [d]The University of New South Wales, New South Wales, Australia. Manuscript received December 2, 2019; revised manuscript received and accepted February 6, 2020.

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*Corresponding author: Tel: + 61 2 9463-2506; fax: +61 2 9463-2053.
E-mail address: usaid.allahwala@gmail.com (U.K. Allahwala).

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at the beginning of the coronary angiogram, including heart rate (HR) and aortic systolic blood pressure (SBP) were recorded, and defined as "starting HR" and "starting SBP."

Analysis of coronary angiography was performed to determine the presence and maturity of collaterals, graded according to the Rentrop classification,[7] where grade 0 = no filling of collateral channels; grade 1 = filling of the side branches of the infarct related artery (IRA); grade 2 = Partial filling of the epicardial vessel of the IRA; grade 3 = complete filling of the IRA. For the analysis, patients were divided into those with poor collateral recruitment (Rentrop grade 0 or 1) and robust collateral recruitment (Rentrop grade 2 or 3) as has been done in previous studies.[8,9] The predominant donor vessel, was defined as the epicardial coronary artery which supplied the greatest number of collaterals to the IRA.

Ischemic time was defined as the time from onset of continuous chest pain, to first angiographic image obtained during PCI. This was chosen rather than balloon time, as the end point was the presence of collaterals at the beginning of the case. A chronic total occlusion (CTO) was defined as the presence of a 100% occlusion in a non-IRA, as has been described previously.[10] Prehospital arrest and ventricular arrhythmia during the case was defined as sustained ventricular arrhythmia with loss of cardiac output necessitating cardiopulmonary resuscitation and/or defibrillation. LV impairment was defined as an LV ejection fraction of ≤50%. Project approval by the local human ethics committee was obtained prior to data analysis.

Continuous variables were presented as means (± standard deviation) or as medians and interquartile ranges, if the distribution of data was not normal. Categorical variables were reported as percentages. The baseline characteristics, PCI procedural findings, and in-hospital outcomes were compared between patients with poor versus robust collateral recruitment. Comparisons between groups were performed using Pearson's chi-square test for all categorical variables and a student's *T* Test for all continuous variables normally distributed or the Kuskal-Wallis *H* test for continuous data not distributed normally.

Multivariate logistic regression analyses were performed to determine variables associated with the recruitment of robust collaterals and in-hospital mortality. The multivariate model was built by forward linear regression, with entry and exit criteria set at the $p < 0.10$. Cumulative event rates were calculated according to the Kaplan-Meier method and compared using the log-rank test. Multivariable Cox's proportional hazards regression was performed to identify predictors of outcomes. All tests were 2-sided, and a $p < 0.05$ was considered statistically significant. Analyses were performed using SPSS (v24, IBM, New York, NewYork).

Results

A total of 1,795 patients were identified during the study period, with 110 patients excluded due to previous coronary artery bypass graft, 13 due to spontaneous coronary artery dissection, 21 due to no image acquired of the non-IRA prior to pPCI, 14 due to no culprit lesion identified and 12 facilitated PCIs. Of the remaining 1,625 patients, 1,280 (78.8%) had poor collateral recruitment, whilst 345 (21.2%) had robust collateral recruitment (Figure 1).

Patients' with robust collateral recruitment were younger (63.1 vs 65.1 years, $p < 0.05$), and had a longer ischemic time (628.5 minutes vs 433.1 minutes, $p < 0.0001$). Cardiovascular risk factors were similar, although patients with robust collaterals were less likely to be treated with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (25.9% vs 31.8%, $p < 0.05$) or an aldosterone antagonist (0% vs 1.6%, $p < 0.05$). Patients with robust collaterals were more likely to have the right coronary artery (RCA) as the IRA compared with the left anterior descending artery or left circumflex (35.3% vs 12.1% vs 14.2%, $p < 0.0001$). Other baseline differences are shown in Table 1.

The presence of robust collaterals was associated with lower in-hospital mortality (2.1% vs 7.6%, $p < 0.0001$) and lower rates of LV impairment (37.6% vs 69.2%, $p < 0.0001$) than in those with poor collaterals (Table 2). One hundred and ninety-six patients underwent rescue PCI for failed thrombolysis, and were less likely to have robust collaterals compared with those undergoing pPCI (12.8% vs 22.7%, $p < 0.0001$). In patients undergoing rescue PCI, presence of robust collaterals was associated with lower rates of LV impairment (50% vs 78.9%, $p < 0.002$) but was not

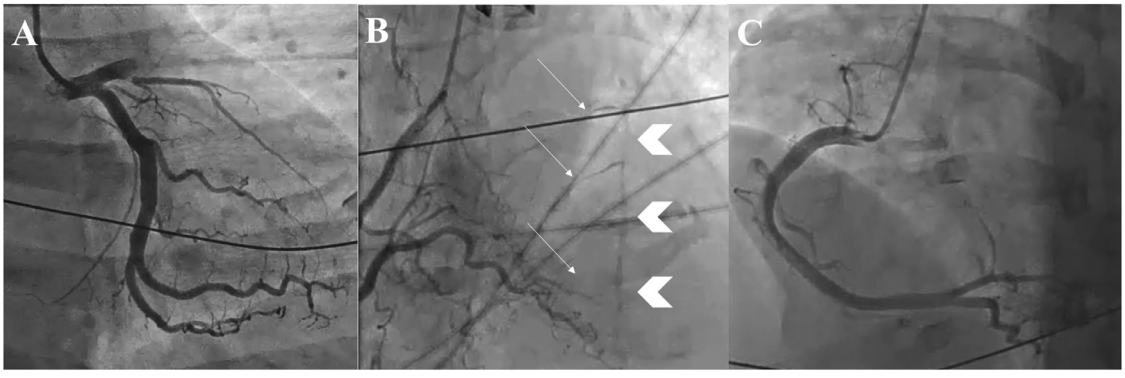

Figure 1. Angiographic appearance of poor and robust collateral recruitment. (A) Coronary angiogram illustrating an occluded left anterior descending artery in the setting of an anterior STEMI. (B) Robust collaterals (Rentrop 2-3) arising from the RCA (thin arrows), opacifying the occluded left anterior descending artery (LAD) in a retrograde manner (solid arrows). (C) No collaterals arising from the RCA in the setting of an anterior STEMI.

Table 1
Baseline characteristics and angiographic findings

Variable	Rentrop 0 or 1 (n=1280)	Rentrop 2 or 3 (n=345)	p value
Age *(years)*	65.1 (± 13.9)	63.1 (± 13.0)	<0.05
Women	23.7%	19.7%	0.13
Body Mass Index *(kg/m^2)*	27.2 (± 4.7)	27.6 (± 4.9)	0.17
Hypertension			
Hypercholesterolemia	46.1%	40.4%	0.07
Smoker	38.7%	35.6%	0.33
Never			0.90
Ex	39.2%	38.9%	
Current	27.6%	27.9%	
Diabetes Mellitus	33.1%	32.1%	
Family History of coronary	16.3%	13.5%	0.26
disease before age 50	27.3%	32.7%	0.06
Ischemic Time *(min)*	433.1 (± 596)	628.5 (± 785)	<0.0001
Medications			
ACE-I/ARB	31.8%	25.9%	<0.05
Beta blockers	13.0%	11.4%	0.45
Statins	22.0%	22.7%	0.77
Aldosterone Antagonist	1.6%	0%	<0.05
Nondyhdropyridine CCB	16.0%	12.4%	0.65
Thrombolysis	13.6%	7.3%	<0.001
Prior angina pectoris	92.9%	91.8%	0.48
Starting Heart Rate (beats/min)	80.0 (±19.8)	78.6 (±18.7)	0.23
Starting Systolic Blood Pressure (mm Hg)	122.4 (± 27.9)	126.9 (± 28.1)	<0.01
Previous stent	10%	10.4%	0.84
Culprit coronary artery			<0.0001
Left anterior descending	674 (87.9%)	93 (12.1%)	
Left circumflex	206 (85.8%)	34 (14.2%)	
Right	400 (64.7%)	218 (35.3%)	
Thrombolysis in Myocardial Infarction Flow >1	39.6%	7.2%	<0.0001
% Stenosis in predominant donor vessel	36.5 (± 23.8)	45.4 (± 25.2)	<0.0001
PCI performed	92.4%	92.5%	1.0
No of stents	1.1 (± 0.6)	1.2 (± 0.7)	<0.05
Length of stent *(mm)*	28.3 (± 14.8)	32.6 (± 17.4)	<0.0001
Presence of Chronic Total Occlusion in non-IRA	5.3%	10.4%	<0.001
Glycoprotein IIb/IIIa Inhibitor use	55.1%	62.6%	<0.05

associated with differences in in-hospital mortality. In those undergoing pPCI, the presence of robust collaterals was associated with lower in-hospital mortality (2.2% vs 7.8%, $p < 0.0001$) and less LV impairment (36.8% vs 67.2%, $p < 0.0001$).

In multivariate regression analysis, the predictors of robust collateral recruitment were younger age (OR:0.85 95%CI:0.75 to 0.97, $p < 0.05$, for every 10 years older), the RCA as the IRA (OR: 3.71 95%CI: 2.64 to 5.22, $p < 0.0001$) TIMI flow 0 or 1 (OR: 10.36 95%CI:5.72 to 18.78, $p < 0.0001$, the presence of a CTO in a remote vessel (OR: 2.65 95%CI: 1.61 to 4.37, $p < 0.001$) and ischemic time (OR: 2.51 95%CI: 1.44 to 4.40, $p < 0.001$ for every hour delay) (Table 3).

The independent predictors of in-hospital mortality were older age (OR: 1.88 for every 10 years; 95%CI: 1.38 to 2.52, $p < 0.0001$), presence of diabetes mellitus (OR:2.53; 95%CI: 1.09 to 5.86, $p < 0.05$), prehospital arrest (OR: 4.59; 95%CI: 2.09 to 10.08 $p < 0.0001$) and LV impairment (OR: 7.71; 95%CI: 2.30 to 25.86, $p < 0.001$), whilst collateral recruitment, the presence of a CTO, and gender were not (Supplementary table 1 & 2).

The mean follow-up for those with robust collaterals was 776.8 days and 751.7 days for those with poor collaterals ($p = 0.62$). The presence of poor collaterals was associated with an increased risk of mortality longer term (HR: 2.1, 95%CI: 1.16 to 3.88, $p < 0.05$) (Figure 2). However, after adjusting for LV impairment, collateral formation did not remain a predictor of long term mortality (Supplementary Table 3).

Discussion

This is a large scale analysis of the presence and prognostic impact of rapidly recruited collaterals in patients presenting with STEMI. 25% of patients undergoing coronary angiography have the ability to recruit sufficient collaterals during balloon occlusion to prevent ischemia.[11] The predictors of rapid recruitment of coronary collaterals have however, remained uncertain. We found that patients with robust collaterals were younger than those with poorer collaterals, similar to prior studies,[12] possibly due to impaired endothelial nitric oxide synthase pathways and increased oxidative stress with older age.[13]

Table 2
Clinical outcomes

Variable	Rentrop 0 or 1 (n=1280)	Rentrop 2 or 3 (n=345)	p value
Cardiac Arrest	11.0%	11.9%	0.63
Inotropes	13.8%	16.5%	0.23
Ventricular arrhythmia during case	6.5%	4.4%	0.16
Left Ventricular Functional impairment*			<0.0001
None/Mild	766 (62.9%)	282 (83.4%)	
Moderate	347 (28.5%)	43 (12.7%)	
Severe	105 (8.6%)	13 (3.8%)	
Left Ventricular Impairment	843 (69.2%)	127 (37.6%)	<0.0001
In-hospital Mortality	7.6%	2.1%	<0.0001
Intensive Care Unit admission	16.4%	13.2%	0.18
Peak Troponin *(ng/L)*	27,722.5 (+/-6.2)	30,333.3 (+/-5.3)	0.44

* 1,556 patients had assessment of left ventricular function performed.

Table 3
Independent predictors of robust coronary collaterals

Variable	OR	95%CI	p value
Right Coronary Artery	3.71	2.64-5.22	<0.0001
Chronic Total Occlusion in a remote vessel	2.65	1.61-4.37	<0.0001
Thrombolysis in Myocardial Infarction Flow <2	10.36	5.72-18.78	<0.001
Ischemic Time (every hour delay)	2.51	1.44-4.40	<0.001
Age (every 10 years older)	0.85	0.75-0.97	<0.05

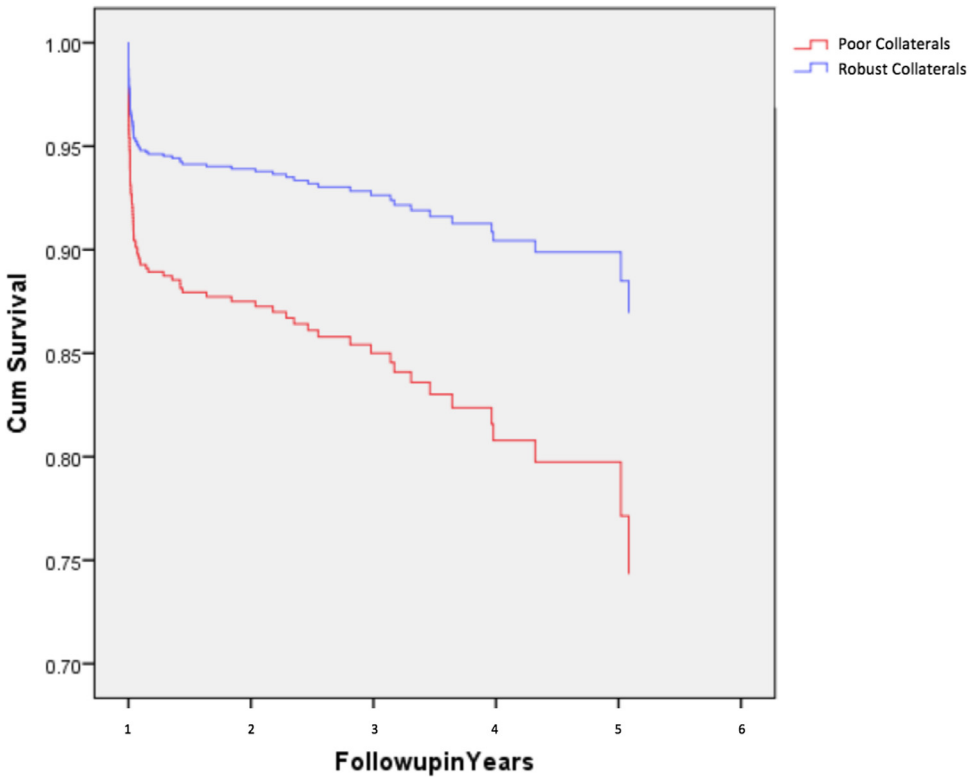

Figure 2. Kaplan Meier curve for survival in patients with robust and poor collaterals.

The recruitment and maturation of coronary collaterals is believed to occur through the process of arteriogenesis, which refers to the transformation of pre-existing arterioles into functional collateral arteries. The primary driver is believed to be an increased pressure gradient and shear stress through these pre-existing channels.[14]

As such, it is unsurprising that in those with robust collaterals, there is a greater ischemic time, which would result in greater shear stress exposure to the immature collaterals. Indeed those with TIMI 2 or 3 flow in the IRA at the onset of angiography were less likely to have robust collaterals, reflecting a reduction in collateral shear stress and flow. Similarly, those with robust collaterals, had a higher initial SBP, which may suggest exposure to higher shear stress.

Robust collaterals were more likely to be seen when the IRA was the RCA, as has been seen in other series.[15] This may reflect the lower resistance myocardium subtended by the RCA, allowing more rapid and robust collateral recruitment. Furthermore, those with a CTO in a remote vessel were more likely to develop robust collaterals. Whilst the hemodynamics and flow undoubtedly contribute to the recruitment of collaterals, certain growth factors have also been implicated in arteriogenesis.[16,17] Conceivably in patients with a CTO, there would be greater levels of these circulating growth factors, which may contribute to more robust collateral recruitment.

In patients with robust collaterals, the donor vessel had a greater degree of luminal stenosis, which is in keeping with previous reports.[18] Whilst previous studies have suggested that a history of angina is a strong predictor of collaterals,[19] we did not see this in our study. This may reflect patient histories of chest pain being unreliable,[20] or else reflect the relatively high incidence of preinfarction angina in our cohort. Furthermore, ischemic preconditioning; the induction of cyclical ischemia to vascular beds around the time of an ischemic insult, has been a proposed mechanism of reducing the degree of infarction.[21] Whilst there have been conflicting reports[22,23] as to whether ischemic preconditioning improves collateral blood flow, it is plausible that the greater degree of donor vessel obstruction, as well as higher rates of CTO may provide preconditioning resulting in improved collateral recruitment.

Both ACE-inhibitors and/or angiotensin receptor blockers and aldosterone antagonist use was associated with poorer collateral recruitment. Previous studies have suggested a negative effect on coronary collateralisation in patients taking ACE-inhibitors,[24,25] possibly due to lower aldosterone levels resulting in lower vascular endothelial growth factor concentrations. Similarly, we found that patients who had robust collaterals were less likely to have received GPIIb/IIIa inhibitors, which although may reflect differing angiographic findings between both groups, may be related to direct platelet effects, whereby activation of platelets has been shown to be associated with poorer collateral flow.[26]

In the present study, robust coronary collaterals were associated with a significantly lower risk of in-hospital mortality and improved myocardial function compared with those with poorer collateral recruitment. This is similar to the findings in other reports,[5,8,9] although Hara et al[6] showed that patients with very robust coronary collaterals (Rentrop grade 3), had a similar mortality rate to those patients without coronary collaterals. The authors argued that this may reflect worse a clinical profile, although there was no benefit observed in their study even after correcting for these confounders. The authors of that study included patients with previous bypass grafts, which may undoubtedly affect shear stress and collateral recruitment and hence interpretation of results. Whilst these results may also reflect ethnic differences between populations, it is possible that the putative advantage of robust collaterals is lost with the greater ischemic time in these patients. Interestingly in our cohort, despite the longer ischemic time seen in patients with robust collaterals, they had improved LV function and lower mortality, suggesting an apparent paradoxical situation in some patients, where greater time of coronary occlusion actually resulted in improved outcomes mediated through robust coronary collateral recruitment. Robust collaterals are associated with less microvascular and endothelial dysfunction,[27] which may provide a mechanism for the improved recovery in ventricular function in this cohort of patients.

The protective effect of acute collateral recruitment seemed to persist following the index event with a maintenance of survival advantage in follow up. We have shown that the ability to recruit collaterals during subsequent infarcts is maintained[28] and hence, it is possible that these patients may maintain a protective effect in the setting of stent thrombosis or repeat infarct. Alternatively, it is possible that the ability to recruit coronary collaterals in the acute setting may extend to recruitment of collaterals in other vascular territories,[29] resulting in a protective mechanism from thrombotic disease elsewhere, which may also improve longer term prognosis. The reasoning for the longer term prognostic impact of robust coronary collaterals requires further investigation.

This study was conducted in a retrospective manner in a single centre, which has inherent limitations. It is possible that some apparent collaterals may not have been visualized due to inadequate time of image acquisition whilst performing angiography of the nonculprit artery during the STEMI. However, robust collaterals are generally seen relatively quickly with a previous study suggesting that collaterals opacify the epicardial vessel in 20 to 30 frames,[30] which in the setting of a cine acquisition of 15 frames per second, does not require prolonged injections and acquisition than standard care.

In this large, detailed analysis of patients presenting with STEMI, the presence of robust collaterals, seen in 20% of patients, was associated with improved LV function. Further research should be undertaken to ascertain the mechanisms by which robust collateral recruitment occurs.

Disclosures

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Authors' Contribution

Usaid K Allahwala: Conceptualization, Methodology, Investigation, Writing - Original Draft; James C Weaver: Methodology, Writing - Review & Editing; Gregory I Nelson: Methodology, Writing - Review & Editing. Daniel Nour: Investigation Max Ray: Investigation Jonathan

L Ciofani: Investigation Michael Ward: Conceptualization; Gemma Figtree; Methodology, Writing - Review & Editing; Peter Hansen; Methodology, Writing - Review & Editing Ravinay Bhindi Methodology, Writing - Review & Editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.02.023.

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