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Review

Insights into the invasive diagnostic challenges of coronary artery vasospasm – A systematic review

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SUMMARY

Coronary provocation testing is an essential diagnostic procedure when evaluating vasospastic angina. Invasive methods using acetylcholine or ergonovine are considered the current gold standard. Despite efforts from global cardiovascular institutions, current protocols vary in dosage, administration time, and procedural approach. In addition, concerns over the specificity of findings and potential complications have limited routine uptake of this procedure in clinical practice. This systematic review evaluates current diagnostic protocols, focusing on invasive provocation testing. We included studies using intracoronary provocation testing with acetylcholine or ergonovine for the assessment of coronary artery vasospasm that detailed specific elements of the procedure (dosage, administration time, etc.) and included ≥50 patients. A total of 28 articles met strict inclusion criteria. Our review highlights the heterogeneity between current diagnostic protocols for invasive provocation testing. We believe standardization of a diagnostic protocol will encourage both current and future cardiologists to incorporate such procedures in the evaluation of variant angina.

Introduction

Coronary artery vasospasm is a transient vasoconstriction of the coronary arteries which plays a significant role in the pathogenesis of vasospastic angina (VSA) and acute coronary syndromes. It was first clinically characterized by Prinzmetal et al. in 1959 as 'variant angina', since it differed to classical exertional angina with episodes occurring at rest and associated with ST elevation [1]. These findings were attributed to coronary artery spasm, which was subsequently demonstrated with the evolution of invasive coronary angiography. Initial literature suggested high mortality, with Caucasian patients having a worse overall survival than their Japanese counterparts [2]. Although the introduction of calcium-channel blockers (CCB) in the 1960s improved the outlook [3], contemporary studies indicate continued high morbidity, with half of adequately treated patients experiencing recurring angina [4,5]. Furthermore, coronary artery vasospasm may lead to myocardial infarction, fatal arrhythmias, or sudden cardiac death [6–9], highlighting the importance of appropriate diagnosis.

The diagnosis of VSA is based on the following three considerations: i) typical clinical presentation of VSA, ii) the evidence of transient ischemia on electrocardiography (ECG) during the angina episode, and iii) the demonstration of a spontaneous or provoked coronary vasospasm (Online Table 1) [1,10–12]. Provocative testing for VSA can be based on a variety of stimuli, both physiological (hyperventilation or cold exposure) or pharmacological [acetylcholine (ACh), ergonovine], which can be used independently or in combination [13–16]. Invasive provocation testing has gained traction in recent years and there is Class IIa recommendation for its use to investigate symptomatic non-obstructive coronary artery disease (NOCA) [11,17,18]. Such investigations allow clinicians to tailor therapy, an approach shown to improve angina symptoms and quality of life [19].

Contemporary literature highlights the superiority of intracoronary ACh and ergonovine in diagnosing VSA. Despite global efforts, protocols for administering these provocative agents are highly diverse across institutions. The lack of consensus may reflect challenges faced with these patients, including atypical clinical presentations, infrequent and

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unpredictable nature of symptoms, and variable response to medical therapy. Furthermore, variations in the propensity of coronary vasoconstriction based on racial differences pose additional hurdles [20].

Researchers have expressed the need for a uniform, evidence-based protocol to assess this cohort of patients accurately [21–26]. The aim of this systematic review is to evaluate the heterogeneity in coronary provocation protocols and their respective evidence-base.

Methods

In 2022, we conducted a search of the PubMed, MEDLINE, Cochrane Library, ProQuest, and Google scholar databases, which included the most recent literature on diagnostic protocols for VSA, focusing on invasive provocation testing. We used the multi-purpose field search for terms (alone and combined) "coronary artery vasospasm", "vasospastic angina", "coronary provocation testing", "vasoreactivity testing", "intracoronary acetylcholine" and "intracoronary ergonovine". We limited our search to humans and the English language. Publications with titles or abstracts which met the inclusion criteria for this systematic review were selected for detailed review. In addition, we looked through the reference tracking of bibliographies and manual searches during the first search to see if there were any additional studies that were relevant. The eligibility of search results was assessed by 2 reviewers independently. Following the removal of obvious unrelated material, the authors analyzed the study abstracts and complete texts independently. A study was included if 1) intracoronary provocation testing with ACh or ergonovine for the assessment of coronary artery vasospasm was undertaken, 2) specific elements of provocation procedure (dosage, administration time, etc.) were discussed 3) ≥50 patients were assessed. Further details regarding inclusion and exclusion criteria are outlined in Online Table 2. The studies were located using the PRISMA approach, and only those that met the inclusion criteria were included (Fig. 1). Any discrepancies at each step were resolved by consensus with a third reviewer.

Results

Of the 194 articles that underwent review, only 28 articles met strict inclusion criteria. In the primary analysis, articles with overlapping patient populations were excluded. If these articles provided additional insight into diagnostic advantages and disadvantages, they were independently referenced during our discussion. Study characteristics are summarised in Table 1 (ACh testing) and Table 2 (ergonovine testing).

Invasive provocative testing

Invasive pharmacological provocation testing is considered the current gold standard (Fig. 2). Recent literature highlights the superiority of

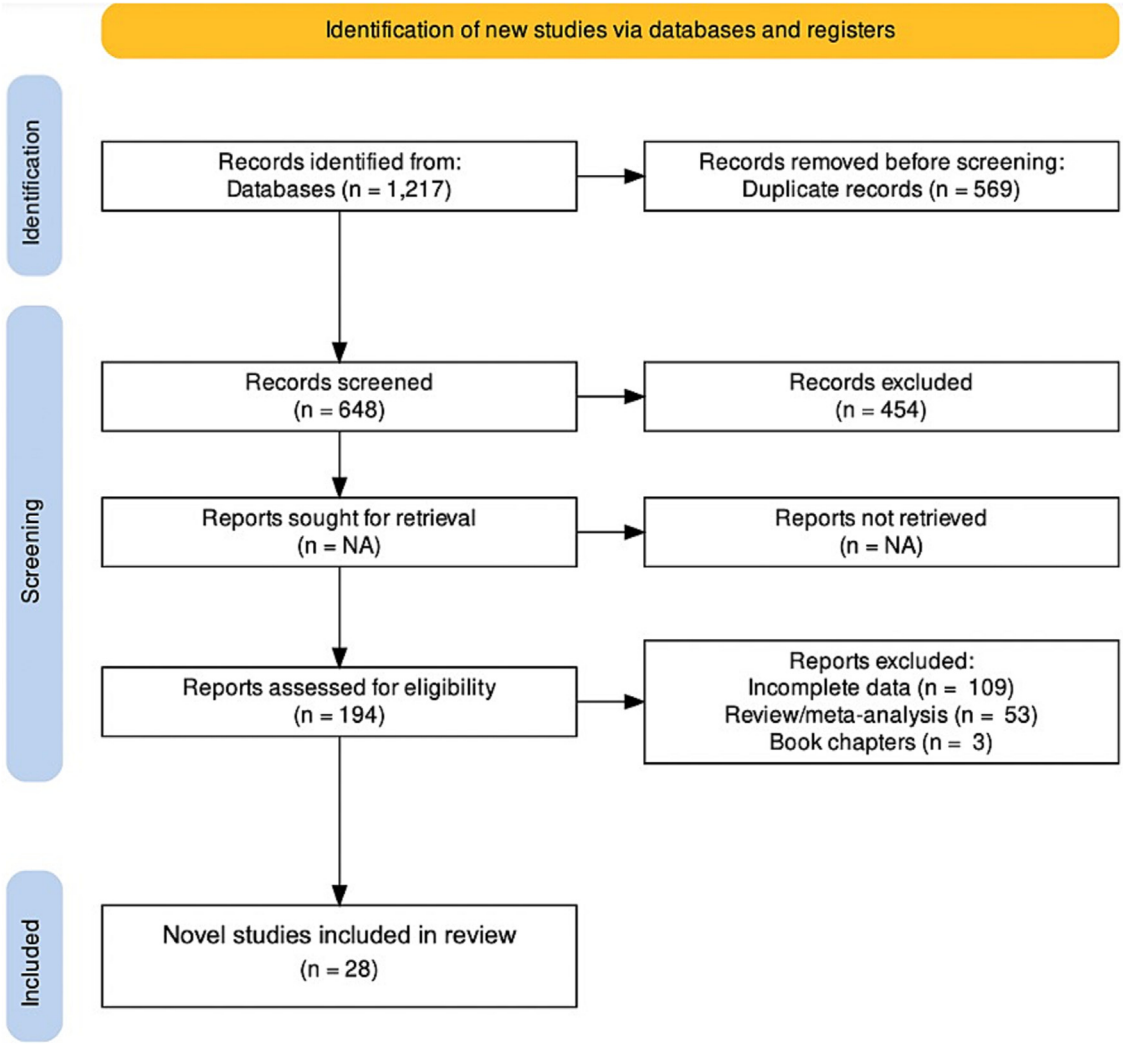

Fig. 1. PRISMA flow chart of literature selection for systematic review.
NA, not available.

Table 1
Protocols for acetylcholine-based provocative testing.

Authors	Year	Country	N	Presentation	Mean age	Gender (F)	ACh dose LCA (ug)	ACh dose RCA (ug)	Administration time (s)	Medication washout duration	Epicardial spasm (%)	Micro-vascular spasm (%)	Positive spasm threshold
Bill et al. [46]	2021	Poland	211	INOCA/MINOCA	60.5	67.8	25-50-100	25-50-75	180	48	46.9	34.1	>90 %
Konst et al. [44]	2021	Netherlands	84	INOCA	56.0	86.9	2-20-100-200	–	60–180	24–48	42.9	NR	>90 %
Montone et al. [47]	2021	Italy	310	INOCA/MINOCA	60.6	56.1	20-50-100-200	20–50	180	24–48	37.7	21.3	>90 %
Pargaonkar et al. [41]	2020	United States	277	INOCA	53.5	77.6	20-50-100-200	–	60	48	–	–	–
Probst et al. [48]	2020	Germany	180	INOCA/MINOCA	62.0	51.7	2-20-100-200	80	180	–	26.1	42.2	>90 %
Sara et al. [37]	2020	United States	1469	INOCA	50.4	65.1	0.182-1.82-18.2 μg/ml	–	180	48	–	–	–
Sueda et al. [53]	2020	Japan	1268	Suspected VSA, post-PCI, others[a]	64.9	28.3	20-50-100-200	20-50-80	20	24	59.3	–	>90 %
Ford et al. [19]	2019	UK	151	INOCA	60.9	73.5	100	50	20	–	37.1	32.5	>90 %
Deyama et al. [51]	2018	Japan	437	Post-myocardial Infarction	64.0	17.8	50-100	50	30	48	44.6	–	>90 %
Tateishi et al. [54]	2018	Japan	529	INOCA/MINOCA	64.1	48.0	20-50-100	20–50	20	48	48.8	–	–
Kim et al. [49]	2018	Korea	5873	INOCA	57.0[a]	53.3	20-50-100	–	60	48			>90 %
Lee et al. [30]	2017	Korea	4644	INOCA	55.2	54.9	20-50-100	–	–	48	13.9	29.5	>75 %
Saito et al. [40]	2017	Japan	216	Suspected VSA	64.0	45.0	20-50-100	20–50	20	48	40.3	–	>90 %
Hoshino et al. [28]	2016	Japan	298	Suspected VSA	64.2	51.7	20-50-100	20–50	60	24	30.9	–	>75 %
Choi et al. [27]	2016	Korea	3155	INOCA	–	–	20-50-100	–	60	72	77.7	–	>70 %
DiFiore et al. [81]	2015	Australia	183	INOCA	54.1	78	25-50-100	25–50	20	48	44.3	32	>90 %
Ong et al. [32]	2014	Germany	847	INOCA/MINOCA	61.8	57.3	2-20-100-200	80	180	48	33.4	24.2	>75 %
Sato et al. [52]	2013	Japan	873	Suspected VSA	63.8	44.2	20-50-100	20–50	20	–	49.6	–	>90 %
Takagi et al. [22]	2013	Japan	713	Suspected VSA	66.0	31.4	20-50-100	20–50	20	24	100[b]		>90 %
Wei et al. [39]	2012	United States	293	INOCA	54	100	0.182-1.82-18.2 μg/ml	–	180	24	7.3	–	>50/70 %
Tio et al. [38]	2002	Netherlands	299	INOCA, obstructive CAD	56	38.1	0.182-1.82-18.2 μg/ml	–	180	24–72	–	–	>50/90 %
Okumura et al. [45]	1988	Japan	163	INOCA, others[a]	57, 54	12.8, 31.1	20-50-100	20–50	20	–	90	–	–

ACh, acetylcholine; CAD, coronary artery disease; LCA, left coronary artery; RCA, right coronary artery; INOCA, ischemia with no obstructive coronary arteries; MINOCA, myocardial infarction with no obstructive coronary arteries; PCI, percutaneous coronary intervention; VSA, vasospastic angina.

[a] Others included valvular heart disease, dilated cardiomyopathy, heart failure, arrhythmia, and others.

[b] This study included patients diagnosed with VSA only.

Table 2
Protocols for Ergonovine-Based Provocative Testing.

Authors	Year	Country	N	Presentation	Mean age	Gender (F)	ER dose LCA (ug)	ER dose RCA (ug)	Administration time (s)	Medication washout duration (h)	Epicardial Spasm (%)	Microvascular Spasm (%)	Positive Spasm Threshold
Kim et al. [82]	2021	Korea	424	Suspected VSA	49.5	59.7	64	40	60	48	11.9	–	>75 %
Ham et al. [67] [a]	2021	Korea	725	Suspected VSA	58.5	44.6	20-40-80	10-20-40	60	1 [c]	37.1	–	>90 %
Sueda et al. [53]	2020	Japan	690	Suspected VSA, post-PCI, others [b]	66.0	36.0	64	40	240	24	28.9	–	>90 %
Aria et al. [68]	2020	Japan	166	Suspected VSA	59.3	33.9	20-20-20	20-20-20	–	24	27.1	–	>90 %
Oh et al. [31]	2019	Korea	158	Suspected VSA	57.4	39.2	10-10-20	10-20-20	60	48	27.8	–	>75 %
Shin et al. [69]	2015	Korea	2129	Suspected VSA	–	55.5	10-20-40	20-40-60	–	48	21.3	–	>90 %
Kim et al. [29]	2014	Korea	85	Suspected VSA	55.4	48.2	10-20-20	10-20-20	60	48	28	–	>75 %

ER, ergonovine; LCA, left coronary artery; RCA, right coronary artery; PCI, percutaneous coronary intervention; VSA, vasospastic angina.
[a] This study analyzed RCA first ergonovine administration.
[b] Others included valvular heart disease, dilated cardiomyopathy, heart failure, arrhythmia, and others.
[c] >5 five half-lives.

intracoronary acetylcholine and ergonovine in diagnosing coronary vasospasm. These agents are administered through an infusion pump or manual bolus injection. Generally, clinicians engage the respective coronary artery with a guiding catheter and perform sequential arteriography to assess a change in vessel diameter following each dose. Following the establishment of the Coronary Vasomotor Disorders International Study Group (COVADIS) VSA angina criteria, most protocols have adopted the definition of coronary spasm as a focal or diffuse narrowing of >90 %, however, some earlier studies have used a lower cut-off of 70 % or 75 % [27–32]. In the case of refractory vasospasm, intracoronary nitroglycerin is promptly injected to avoid prolonged ischemia. However, uncertainty surrounding the optimal dose and infusion rate has led to varying global practices. *Tables* 1 and 2 highlight the lack of uniformity when using intracoronary ACh and ergonovine, respectively.

Acetylcholine-based provocative testing

ACh is a vasoactive substance that provokes vasospasm via cholinergic receptors on vascular smooth muscle cells [33]. When ACh is administered as a low-dose infusion in patients with a healthy endothelium, a vasodilatory response is observed due to the endothelial release of NO. [34] In contrast, dysfunctional endothelium cannot release sufficient NO to overcome the stimulated vascular smooth muscle muscarinic receptors leading to mild vasoconstriction, typically <30 % constriction [34]. In ACh provocative spasm testing, rapid bolus administration of high-dose ACh is used, producing severe vasoconstriction (i.e. >90 %) in patients with a predisposition to coronary vasomotor hyperreactivity. Adopting these mechanistic considerations, along with an established safety track record [35] has made ACh provocation testing the most commonly used diagnostic test for VSA. Nevertheless, the heterogeneity in dosage and administration time has limited the understanding and acceptance of a uniform protocol amongst cardiologists.

Dosage and coronary artery predominance

Doses vary for left (LCA) and right (RCA) coronary arteries but are uniformly higher for the left system *(*Table 1*)*. The maximum dosage for the LCA is 200 μg, and RCA is 80 μg, respectively. Sueda et al. suggested that a dose of 200 μg improved diagnostic utility, especially in patients with high clinical suspicion of VSA and no provoked spasm with smaller doses [36]. Regardless, the propensity for pseudo-positive reactions at such doses may reduce diagnostic specificity. Alternatively, the WISE study employed a protocol of sequential intracoronary (IC) infusions of incremental ACh doses (0.182–1.82-18.2 mg/mL), as did Tio and Sara et al. [37–39]. The CorMica trial emulated this protocol but also added an ACh bolus of 100 μg (LCA) and 50 μg (RCA) [19]. Most protocols have an incremental dosing regimen and commence testing in the LCA. In contrast, others have focused on testing the RCA first and terminating the procedure afterwards if spasm is identified [28]. Saito et al. proposed omission of the 50 μg dose of ACh in the LCA if there was little coronary artery constriction by 20 μg, leading to reduced contrast volume and procedural time [40]. Interestingly, men and women had different responses to ACh, with men demonstrating a minimal lumen diameter dose-relationship with doses to 200 μg while women had little changes with doses above 50 μg [41]. These findings suggested an incremental gender-adjusted dosage regimen could improve the diagnostic utility of provocation testing.

The possible predominance of coronary spasm within specific coronary arteries was explored by Sueda and Kohno [42]. In a retrospective analysis of 1392 patients who had undergone ACh-based provocative testing, the proportion of spasm involving the left circumflex artery (28.3 %) was significantly lower ($p < 0.001$) than that involving the RCA (73.3 %) and the left anterior descending artery (72 %) [42]. These findings were confirmed by subsequent studies from Korea [30,43]. These results suggested that the left circumflex artery might be less responsive to ACh-based provocative testing. Notably, several studies

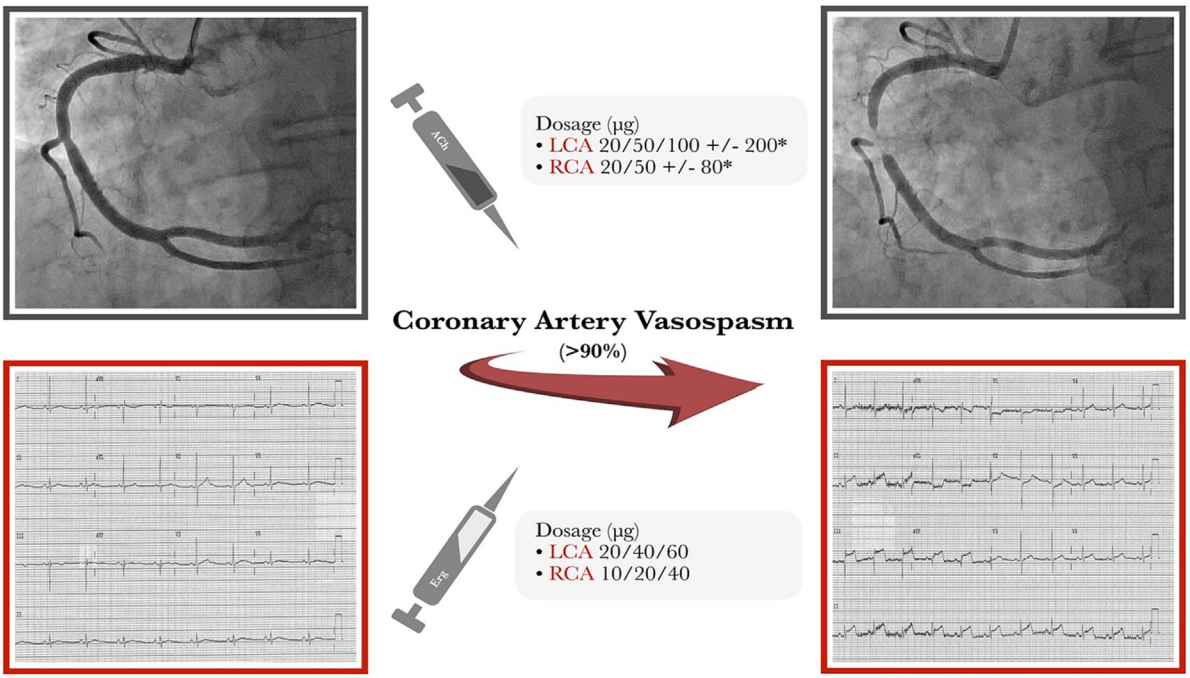

Fig. 2. Invasive angiographic evidence of focal right coronary artery spasm with concomitant inferior ST elevation on electrocardiogram. Invasive provocation testing dosage regimens with acetylcholine (ACh) and ergonovine (Erg) for diagnostic evaluation are illustrated above.
LCA, left coronary artery; RCA, right coronary artery.

have avoided provocative testing in the RCA altogether [30,37,41,44]. Despite the reduction in procedural time and contrast administration, this can neglect the presence of multivessel spasm, a known poor prognostic marker [22]. Furthermore, single-vessel testing may reduce diagnostic yield.

Administration time

In the study that validated the ACh provocative spasm protocol, Okumura et al. administered 20, 50, and 100 μg in the LCA and 20 and 50 μg into the RCA, as serial 20-s boluses. In this landmark study, patients fulfilling the variant angina clinical criteria for spontaneous vasospastic episodes, along with a negative control cohort (i.e. patients with cardiomyopathy, arrhythmia, valvular disease, hypertension, and congenital heart disease) were studied using this ACh administration protocol [45]. The study demonstrated high sensitivity (90 %) and specificity (99 %) with the protocol, thereby validating its use for the diagnosis of VSA. Although derivations of this protocol have been described, they have not been validated against the native disorder characterized by spontaneous episodes of spasm. The heterogeneity in ACh administration protocols has in part arisen from clinical research studies designed to assess functional endothelial integrity. These protocols utilize 2–3 min low-dose (<20 μg) ACh infusions and have been utilized in multiple studies [32,37–39,46–48]. Other protocols described longer manual injections of 60 s [27,41,49]. Sueda and Kohno reported the results of a study including 30 patients with ischemic heart disease who first received an IC 20-s ACh injection followed by a 3-min infusion. They noted a positive spasm provocation in 73.3 % vs 33.3 % ($p < 0.05$) patients, respectively [50]. These results suggest that the administration time of IC acetylcholine may affect the results of provocative testing. Limitations of this study included a small sample size with majority being male smokers (83.3 % and 76.7 %, respectively) [50].

Temporary pacemaker insertion and procedural approach

The insertion of a temporary pacemaker (TPW) during provocative testing has also varied amongst international research groups. Many institutions advocate for the insertion of a TPW upfront [22,51–54]. Unsurprisingly, a back-up pacing rhythm was significantly higher during ACh administration into the RCA, especially during a rapid 20-s injection compared to a 3-min infusion (63.3 % vs 23.3 %; $p < 0.01$) [50]. Despite a marginal increase in overall procedural time, it may avoid a serious complication. On the other hand, Ong et al. preferred to avoid a TPW and suggested transient atrioventricular block almost always resolved within seconds of reducing the speed of administration [32]. However, it is uncertain whether this approach, with potentially slower administration of the provocation agent, will decrease the diagnostic yield.

The optimal procedural approach site for both artery and vein (assuming insertion of a temporary pacemaker) was investigated by Sueda and Kohno [55]. They retrospectively analyzed the outcomes of 1829 ACh-based provocative tests according to vascular access routes, including: i) femoral artery and femoral vein (16 %); ii) brachial artery and femoral vein (27.2 %); iii) brachial artery and brachial vein (32.2 %); iv) radial artery and brachial vein (13.8 %), and v) radial artery and femoral vein (9.6 %) [55]. Although there was no statistical difference in procedural-related major complications between these groups, the investigators found that the radial artery and brachial vein combination provided the most comfort for both operators and patients without sacrificing diagnostic utility [55]. Current guidelines do not specify a preferred approach, although the use of intra-arterial vasodilators (e.g. nitroglycerin, verapamil) and operator experience are key influencing factors [56]. Intra-arterial vasodilators are routinely administered for trans-radial access to increase radial artery size and reduce radial spasm [57]. However, these agents may diminish the diagnostic yield of provocation testing when administered during the index procedure. Verapamil is generally avoided given its relatively long half-life; however, nitroglycerin is required during concomitant coronary physiology testing. Despite its rapid half-life (approximately 3 min) [58], the residual effect of nitroglycerin on the sensitivity of coronary provocation testing is unclear. Current practice is based on expert consensus although further studies are required to investigate the potential confounding effect of vasodilators on these provocation studies [59].

Table 3
Common vasodilators that should be withheld prior to vasoreactivity testing.

Name	Half-life (hours)	Washout period (hours)[a]
Calcium channel blockers		
Amlodipine	35–50	191
Felodipine	20–25	101
Lercanidipine	8–10	40
Verapamil (IR)	5–12	38
Diltiazem	3–5	18
Nifedipine	1.5–3.5	11
Nitrates		
Nicorandil	1	5
Isosorbide mononitrate	5	23
Nitro-glycerine (Transdermal)	1	5
Nitro-glycerine (SL)	<10 min	<1
Nitro-glycerine (IV)	<10 min	<1
Nitro-glycerine (IC)	<10 min	<1

[a] Approximately - based on 4–5 half-lives given 94–97 % of a drug will be eliminated. Hence, the plasma concentration of a given drug will be below a clinically relevant concentration [83].

Ergonovine-based provocative testing

Ergonovine is a vasoactive substance that possibly acts via the serotonergic receptors in vascular smooth cells leading to vasoconstriction [60,61]. In 1972, the Cleveland Clinic first administered ergonovine during cardiac catheterization to provoke coronary spasm [62]. Initially, ergonovine provocative testing involved bedside intravenous administration, which was simple and widely available but led to safety concerns [63]. In particular, a report of three deaths (ventricular arrhythmias) with intravenous ergonovine-based bedside testing led to the emergence of intracoronary cardiac catheterization laboratory-based administration [64–66]. As highlighted in Table 2, administration methods and dosage regimens vary amongst institutions - these range from continuous IC administration, bolus injections, and different maximal dosages.

Dosage and administration time

Similar to ACh provocation testing, ergonovine doses vary between the LCA and RCA but are consistently higher for the left system. The maximum IC dosage for the LCA is 80 μg, and RCA is 60 μg, respectively [67]. Most protocols adhere to an incremental dosing regimen starting at a minimum dose of 10–20 μg for either coronary artery [29,31,59,67–69]. As illustrated in Table 2, the exact dosage regimen varies amongst different research groups, although most include three incremental dosages per coronary artery.

The administration time for ergonovine provocation testing has significantly reduced over the past decade. As recommended by the Japanese Circulation Society (JCS) Working Group, Sueda used a 240-s infusion for the LCA and RCA [53]. There was a 5-min interval between injections, and a single bolus injection was not recommended. In recent years, institutions have moved toward a 60-s infusion with a 100–180 s interval between injections [29,31,67]. These current protocols sustain a high diagnostic yield without any significant complications. However, these regimens essentially included patients with a high clinical suspicion of ischemic chest pain without a control comparison group.

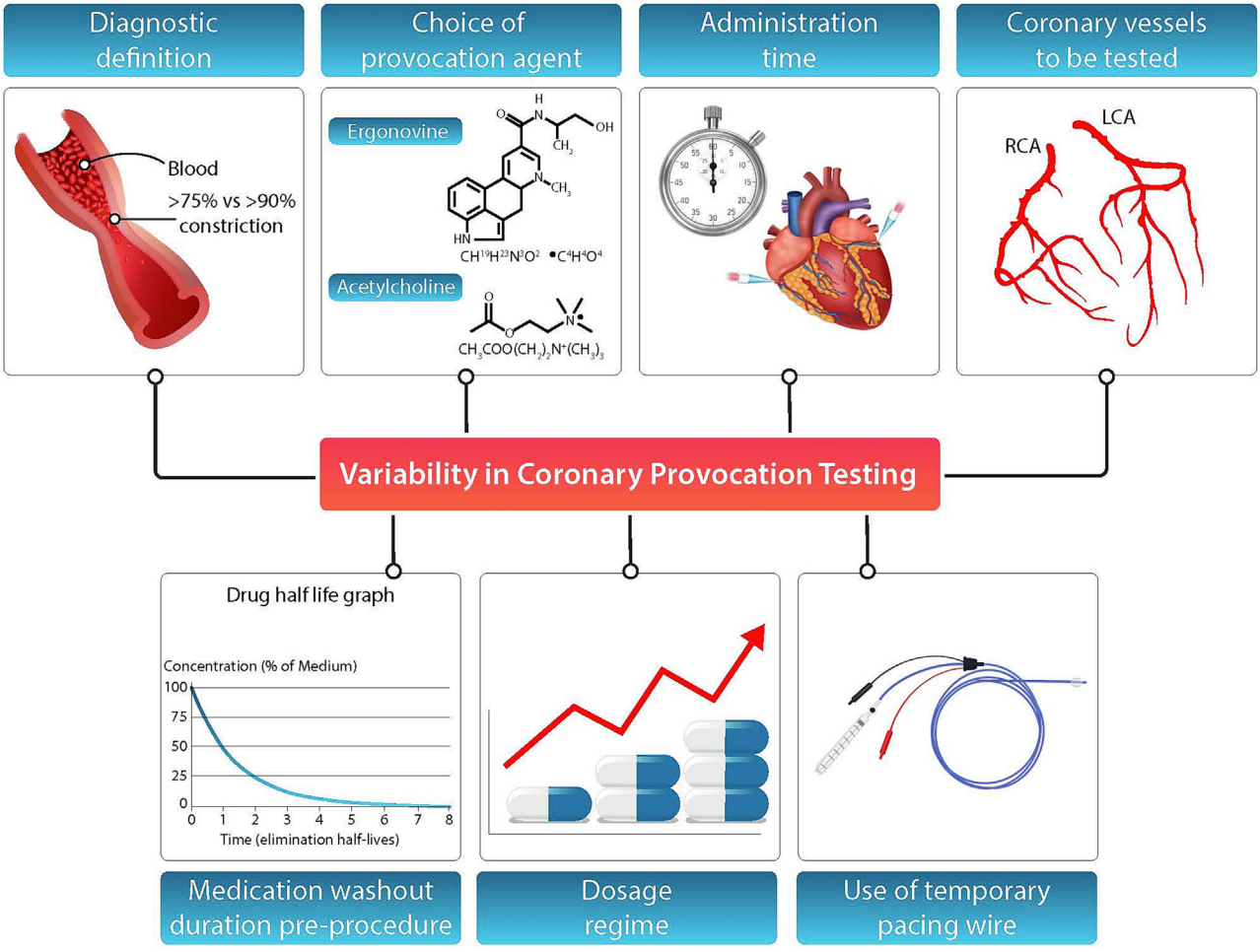

Fig. 3. Key factors underlying the variability in coronary provocation testing.
LCA, left coronary artery; RCA, right coronary artery.

Coronary artery predominance

Shin et al. conducted the most extensive study for ergonovine-based provocative testing [69]. A total of 2129 patients from the VA-Korea (Vasospastic Angina in Korea) registry were evaluated in 11 cardiovascular centers. Testing was commenced in the LCA at incremental dosages of 20/40/60 μg, followed by the RCA at a lower dosage of 10/20/40 μg. Interestingly, coronary spasm was most frequently provoked in the RCA only (57.7 %) in patients with single-vessel spasm (71.8 %) [69]. Subsequently, Ham et al. investigated an RCA-first approach given the lower dosage required and lack of concrete evidence supporting the conventional LCA-first approach [67]. In 725 patients, they found that an RCA-first approach was equally effective at diagnosing coronary spasm [67]. The authors believed this approach was feasible and an RCA-alone approach could be considered in the absence of high-risk features (syncope, cardiac arrest), an intermediate provocation response or strong clinical suspicion. Like ACh provocation testing, the left circumflex artery also had a lower incidence of vasospasm when using ergonovine [70]. This differential sensitivity may be secondary to lower expression of serotonergic and cholinergic receptors or, as previously mentioned, a lower proportion of subtended myocardium.

Comparing acetylcholine and ergonovine invasive provocative testing

Pharmacological provocation testing should be performed in the morning, and patients are requested to discontinue medications (including calcium channel blockers, nicorandil, and long-acting nitrates) for 24 to 72 h. Most published studies followed this regimen (Tables 1 and 2), although further studies are required to determine best practice. As highlighted in Table 3, long-acting CCBs may require a longer washout period than initially proposed [71]. In addition, standard contraindications apply, including left main stenosis (>50 %), triple-vessel disease, two-vessel disease with total occlusion, heart failure (New York Heart Association Class III or IV), renal failure (creatinine > 2.0 mg/dl), and the presence of spontaneous spasm. Severe asthma is a stated contraindication for ACh use, although Sueda did perform ACh vasoreactivity testing in 13 such patients without any complications [72].

A recent retrospective analysis involving 2500 patients from a single center in Japan revealed that ACh-based provocative testing resulted in more frequent detection of coronary artery spasm than ergonovine. (48.7 % for acetylcholine vs 28.9 % for ergonovine; $p < 0.001$) [53]. Similar results were portrayed by an extensive multi-center cohort study of 21, 512 Japanese patients [73]. Notably, this found that 0.9 % of patients undergoing ACh-based provocative testing required urgent cardiac procedures to address procedural complications, a significantly higher proportion than the ergonovine group (0.4 %; $p < 0.001$) [73]. Arrhythmias requiring defibrillation accounted for the majority of procedural complications. As described by Suzuki et al., the propensity of ACh to prolong QT dispersion may predispose such patients to provocation-related ventricular arrhythmias [74]. Nevertheless, both pharmacological agents are generally safe without irreversible complications. The rate of major complications including death, myocardial infarction, ventricular fibrillation/sustained ventricular tachycardia, refractory coronary artery spasm, coronary dissection, cardiac tamponade, or shock has been reported to be <1 % [35,75]. Of note, there has been no ACh-induced mortality although this did occur with early ergonovine studies [16,76].

Preference for acetylcholine or ergonovine provocation testing is an ongoing debate. It may be influenced by a relatively faster onset of action and reversibility of ACh-induced spasm versus a relatively lower incidence of arrhythmias with ergonovine [21,25,31,53]. In addition, selection between these agents could be affected by gender (ACh favored in females) and age (ergonovine favored in younger patients) [25]. Furthermore, the presence of chronic kidney disease may deter standard incremental ACh testing given excessive contrast exposure. Clinicians may also consider a combination of both ACh and ergonovine provocation testing. Sueda et al. used sequential injections of both ACh and ergonovine in a small cohort of patients; a method that induced spasm in almost 10 % of patients who initially tested negative [24]. This approach was safe but it is uncertain whether this approach should be considered in patients with a high clinical suspicion of VSA.

Non-invasive provocative testing

Non-invasive, non-pharmacological provocative testing has a minor role in the diagnostic algorithm for VSA. The JCS 2013 guidelines recommend hyperventilation and exercise as valid methods of non-pharmacological provocative testing when coupled with ECG [59]. It proposes a target respiratory rate of 25 per minute (for up to 6 min) with discontinuation of the test in the presence of angina or significant ECG changes. The COVADIS consensus also acknowledges hyperventilation as a valid option, but cold pressor testing is recommended over exercise [12].

Pharmacological, non-invasive testing has also been explored. In 1983, Waters et al. reported a better sensitivity with intravenous ergonovine compared with non-pharmacological techniques [77]. Subsequently, the safety of intravenous ergonovine with echocardiography was demonstrated by Song et al. in a retrospective analysis of 1372 patients [78]. Overall, 31 % of the patients had positive results correlating to a sensitivity and specificity of 93 % and 91 %, respectively [78]. More recently, Om Sang et al. [79] suggested ergonovine echocardiography could replace invasive spasm provocation testing, a notion that is contrary to the recommendations by the JCS and COVADIS groups [12,59]. In this study, 14, 012 patients were assessed with ergonovine echocardiography using a maximum of 350 μg intravenous ergonovine in bolus doses of 50 or 100 μg after a 5-min interval. The study found that 15.3 % of patients had coronary spasm demonstrated by ECG changes or reversible regional wall motion abnormalities on echocardiography [79]. Despite these results, limitations for ergonovine echocardiography included: the inability to administer intracoronary nitroglycerin in the setting of refractory spasm, no temporary pacemaker backup, and available acoustic windows. Further data on safety, sensitivity, and specificity are required to determine its true role in clinical practice.

Conclusion and future directions

Invasive provocation testing with ACh and ergonovine has emerged as the gold standard for diagnosing coronary artery vasospasm. While various protocols exist amongst global cardiovascular institutions, the COVADIS working group and JCS recommendations for ACh testing have gained popularity. Incremental intracoronary ACh injections have demonstrated good diagnostic capability when administrated over 20 s, with doses up to 100 μg in the LCA and 50 μg in the RCA artery [45]. Reports from Europe and Japan suggest that higher doses of 200 μg in the LCA and 80 μg in the RCA can be considered in patients with a lower disease burden, however, the accumulation of evidence is limited [32,80].

Despite promising results of invasive provocation testing, its variability in practice remains a key challenge to wider clinical acceptance (Fig. 3). To overcome this, future studies should focus on establishing a uniform diagnostic definition, standardizing pre-procedure medication washout duration, and addressing nuances during testing (i.e. pharmacological agent, administration route and time, dosage regimen, vessels tested, and back-up TPW). In addition, incorporating negative control populations in such studies would provide objective evidence for the sensitivity and specificity of different regimens. Adopting a standardized and practical diagnostic protocol will encourage cardiologists to incorporate this procedure for the evaluation of VSA.

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Declaration of competing interest

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Appendix A. Supplementary data

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