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CPAP reduces hypercoagulability, as assessed by thromboelastography, in severe obstructive sleep apnoea☆

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ABSTRACT

Obstructive sleep apnoea (OSA) is associated with increased cardiovascular morbidity and mortality and hypercoagulability may be an underlying factor. We tested the hypotheses that patients with severe OSA are hypercoagulable and that two weeks of continuous positive airway pressure (CPAP) treatment reduces this hypercoagulability. In a prospective crossover study, twelve patients were randomized to either CPAP or no-CPAP for two weeks, a one week washout period, and then the other testing period for two weeks. Thromboelastography was used to assess coagulability at the start and end of each period and the apnoea-hypopnea indices (AHI) were measured at the end of each period. At baseline, ten patients had, compared to reference values, shorter clotting times, six increased rate of clot formation, twelve increased clot strength, and ten increased clotting indices. CPAP significantly reduced AHI ($p = 0.0003$), clot strength ($p = 0.019$) and clotting index ($p = 0.014$). Hypercoagulability in patients with OSA can be detected by thromboelastography, and is reduced by CPAP.

1. Introduction

Obstructive sleep apnoea (OSA) is a highly prevalent sleep disorder, affecting 24% of adult males and 9% of adult females in North America and is even more prevalent among the elderly (Young et al., 2002). The underlying pathophysiological mechanisms by which OSA increases cardiovascular morbidity and mortality are not fully understood. Several common risk factors, including obesity, increasing age, smoking, hypertension, diabetes mellitus and post-menopausal status (Yazdan-Ashoori and Baranchuk, 2011; Zaigham and Zaigham, 2010) exist for both OSA and cardiovascular disease. In recent reviews, hypercoagulability is included as a factor predisposing to increased morbidity and mortality in OSA (Bagai, 2010; Fava et al., 2011), particularly strokes (Di Tullio et al., 2008) and myocardial infarction (Scarabin et al., 1998; Tzoulaki et al., 2007). Hypoxia, a critical pathophysiological element that leads to augmentation of sympathetic activity in association with OSA, increases the levels of various markers of inflammation, oxidative stress, and procoagulant activity (Lurie, 2011; Somers et al., 1995).

Several studies have revealed elevated or upregulated individual components of the haemostatic system in patients with OSA, including enhanced platelet activation, increased plasma levels of tissue factor, von Willebrand factor (VWF) and fibrinogen levels (Akinnusi et al., 2009; Bokinsky et al., 1995; El Solh et al., 2008; Liak and Fitzpatrick, 2011; Robinson et al., 2004). However, little information is known about the value of thromboelastography (TEG) as a global haemostatic tool in OSA.

TEG, unlike basic haemostatic screening tests such as prothrombin time (PT) and activated partial thromboplastin time (APTT), or coagulation factor assays, provides information about the full spectrum of the haemostatic process, starting from the initial formation of fibrin threads until lysis of the clot. To our knowledge, only one study has used TEG to assess coagulability in patients with OSA (Guardiola et al., 2001). In that study, the authors assessed only the latency of clot formation (*R* time). Moreover, they used healthy subjects as controls; as the authors acknowledged, this did not eliminate any contributions to coagulability of such common and confounding comorbidities as obesity, hypertension and metabolic syndrome.

In this study, we analysed all TEG parameters to assess haemostatic status in patients with severe OSA. We also evaluated, using

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a randomized crossover protocol to eliminate confounding variables, the effects of 2 weeks of CPAP on coagulability. We tested the hypotheses that patients with severe OSA are hypercoagulable and that CPAP treatment reduces this hypercoagulability.

2. Materials and methods

2.1. Study subjects

Thirteen patients, aged 33–61 years, with severe OSA (apnoea-hypopnea index (AHI) ≥ 30 events/h), participated in the study following informed consent. All subjects were initially diagnosed in the sleep disorders laboratory at Kingston General Hospital. Seven patients had full diagnostic polysomnography and the other five were diagnosed via a split-night protocol. With respect to patients' use of CPAP therapy prior to the study, three had used their CPAP devices for less than 1 month, and the other nine had used it for longer than 1 month but less than 3 months. Patients who had diagnostic PSGs returned to the sleep lab for a subsequent therapeutic PSG; those who underwent a split-night protocol were, of course, titrated during the second part of the night. None had a positive history of chronic obstructive pulmonary disease, use of anticoagulants or antiplatelet agents, or reported use of herbal remedies that may influence haemostasis. The study protocol was reviewed and approved by the Health Science Research Ethics Board at Queen's University in Kingston, Ontario, Canada.

2.2. Study protocol

The study used a prospective, randomized, crossover design to examine the effect of CPAP on haemostasis in patients with a diagnosis of severe OSA. A crossover protocol was used to eliminate the influence of confounding comorbidities in patients with OSA (Coccagna et al., 2006; Jean-Louis et al., 2008; Lam and Ip, 2007) and to increase statistical power. Participation in the study required patients to take part in two separate testing limbs, separated by a 1 week washout period. On one testing limb, patients were asked to use CPAP treatment continuously (at the optimal pressure setting) for 2 weeks (treatment limb), and on the other, the CPAP unit was removed for two weeks. The order of the testing limbs (treatment or control) was randomly assigned using a computer-generated table of random numbers. AHI was measured at the end of each testing limb via at-home sleep studies. All subjects in both arms refrained from using their CPAP therapy during the washout period. The two potential randomized groups (CPAP/No-CPAP or No-CPAP/CPAP) are detailed in Fig. 1, along with a timeline for TEG and at-home sleep studies. In this crossover study, patients acted as their own controls.

TEG was performed at the beginning and at the end of each testing limb, as the main outcome measure was the change in haemostasis between the treatment and control limbs of the study. A venous blood sample was taken at the same time of day for each patient in order to standardize the measurement against any confounding circadian effects. Sleep data were also measured at the end of each testing limb to ensure either adherence to or discontinuation of CPAP treatment. The personnel performing the TEG measurements, those scoring the sleep data as well as phlebotomists, were blinded as to the testing limbs.

2.3. Thromboelastography

TEG (TEG 5000, Haemoscope; Braintree, MA, USA) was performed according to the manufacturer's instructions. The citrated whole blood sample (340 μL) was recalcified with 20 μL 0.2 M $CaCl_2$ and placed into the TEG cup. Major coagulation parameters calculated by the manufacturer's software included the following: (i) *R* time, time for formation of the initial fibrin threads (normal = 9–27 min); (ii) alpha (α) angle, the rapidity with which the clot forms (normal = 22–58°); (iii) *K* time, the time until the clot reaches a certain strength (normal = 2–9 min); (iv) MA, maximum amplitude or the clot's maximum strength (normal = 44–64 mm); and (v) CI, the clotting index or the overall clotting activity based on the previous four parameters (normal = −3 to +3). Together, α angle and *K* time reflect fibrin build-up. LY30 is a measurement of fibrinolysis that is determined by the rate of fall in amplitude 30 min after the peak is reached, and when lysis of the clot starts. Each analysis was performed on the same device within 30 min of sample collection, lasted at least 1 h, and all manipulations were identical for all samples. Hypercoagulability is defined by a shortening of *R* time and increases in α angle, MA and CI. Normal reference values used in this study are in accordance with the manufacturer's instructions (http://www.haemoscope.com/) in which age and sex for normal individuals were considered. Because each patient acted as his or her own control, the effects of confounding comorbidities affecting coagulability were eliminated.

2.4. At-home sleep study

The at-home sleep data were collected utilizing a MediByte device (Braebon Medical Corporation; Carp, ON, Canada), a validated Level III portable monitor for sleep apnoea (Driver et al., 2011). It consists of a nasal cannula pressure transducer (airflow), a finger pulse oximetry sensor (SpO_2 and heart rate), two respiratory effort bands (chest and abdomen), and a body position sensor. The device records up to 24 h of continuous digital data, which are then downloaded to a software program (Pursuit; Braebon Medical Corporation; Carp, ON, Canada) for manual scoring by a trained technologist.

2.5. Statistical analysis

Data were entered into a spreadsheet and imported into IBM SPSS Statistics (Version 19.0; Armonk, NY, USA) for statistical analysis. To facilitate paired analyses, data were then reordered so that matching testing limbs for each randomized group were aligned: (i) Time 1 and Time 2 data for the CPAP/No-CPAP group were aligned with Time 3 and Time 4 data from the No-CPAP/CPAP group; and (ii) Time 3 and Time 4 data for the CPAP/No-CPAP group were aligned with Time 1 and Time 2 data from the No-CPAP/CPAP group. Due to the limited sample size, non-parametric tests were conducted to assess for significance. Prior to data analysis, independent samples testing (Mann–Whitney *U*) was used to compare the values for the CPAP/No-CPAP group and the No-CPAP/CPAP group to assess for order effects. Paired samples testing (Wilcoxon Signed Ranks test) was then used to assess changes in TEG parameters within the treatment limb. Change scores were also calculated for the TEG parameters (post-treatment minus pre-treatment) within the treatment limb, and difference scores were calculated for the OSA values (measured only twice, hence post-treatment limb minus post-control limb); the correlation between the change in TEG and the difference in OSA was assessed using Spearman rank correlation.

3. Results

3.1. Patient characteristics

We recruited 13 patients (8 males and 5 females), aged 33–61 years, previously diagnosed with severe OSA (AHI ≥ 30 events/h). One patient was excluded because of non-adherence to the study

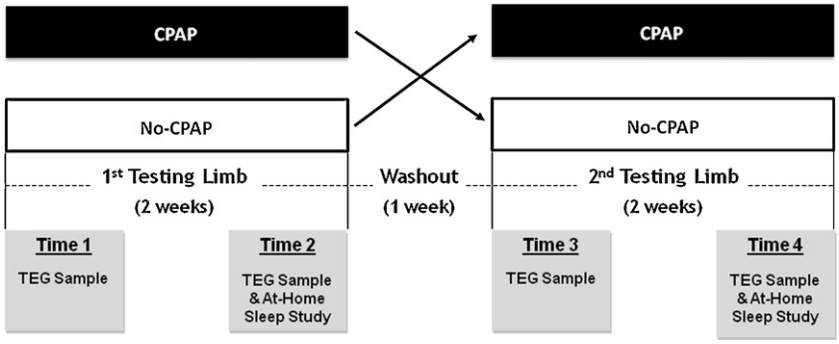

Fig. 1. Study protocol showing the crossover limbs. Twelve patients participated in the entire study (6 patients per randomization order). TEG was performed at the start and end of each limb and AHI was measured at the end of each limb.

protocol. The body mass indices (BMI) of the 12 remaining patients ranged between 27.3–54.6 kg/m^2. Patient characteristics and AHI data are provided in Table 1. It must be noted that the AHI on the portable study was lower than that recorded in the sleep lab at time of diagnosis. Portable devices tend to underscore the AHI because they measure respiratory events rather than sleep time (Driver et al., 2011).

3.2. Baseline coagulability in patients with severe OSA

Representative normal and hypercoagulable TEG traces from our patients are shown in Fig. 2. To analyse pre-treatment scores, we examined TEG parameters when patients were not on CPAP (i.e., Times 1 and 2 in the No-CPAP/CPAP group and Times 1 and 4 in the CPAP/No-CPAP group). *R* was shorter in 10 of 12, and α angle, MA and CI increased in 6 of 12, all 12, and 9 of 12 patients, respectively (Table 2). As demonstrated in Table 2, MA (clot strength) showed the most abnormal value compared to other parameters while α angle (rate of clot formation) the least. In fact, the values for α angle were only "high normal" and also showed the greatest inter-individual variations among patients. Values for LY30 were all within the normal range (data not shown), indicating that fibrinolysis may not be affected in severe OSA. Independent samples testing (Mann–Whitney *U*) indicated that the groups were equivalent at each of the analysis points, suggesting that the wash-out period was effective and that there were no order effects.

3.3. Effect of CPAP treatment on AHI and blood coagulability

To analyse the effect of CPAP on OSA, we measured AHI at the end of each testing limb in both groups. AHI was significantly greater at the end of the control (no CPAP) limb compared to the treatment (CPAP) limb (average ± SD: 33.8 ± 18.9 versus 6.0 ± 5.7 events/h, respectively; $p = 0.0003$). Individual AHI data are shown in Table 1.

Two weeks of CPAP treatment significantly reduced MA from 70 to 66.0 mm (6%) and CI from 3.5 to 2.9 (17%). There was also a non-significant trend towards an increase in *R* time with CPAP, from 6.6 to 7.2 min (*R* time was normalised by CPAP). CPAP had no effect on α angle (Fig. 3).

3.4. Correlations between coagulability and the CPAP induced improvement in AHI

To evaluate the relation between the improvement in AHI (measured at the end of each treatment limb) and change in TEG parameters (measured at the beginning and end of treatment), we performed non-parametric correlations; these were not statistically significant for *R* time ($r = 0.301$), α angle ($r = 0.007$), MA ($r = 0.119$) and CI ($r = -0.130$) with respective *p*-values of 0.34, 0.98, 0.71, and 0.69.

4. Discussion

In this study, patients with severe OSA were hypercoagulable on the basis of TEG. In each of the 12 patients, at least one TEG parameter indicated hypercoagulability. MA showed the most evident change (all 12 patients had abnormally increased MA with an average 68 compared to the reference 46 mm value), indicating that an increased fibrinogen level and/or enhanced platelet function were likely the main haemostatic changes. The degree

Table 1
Clinical and demographic data for the study participants. Patients 1, 4, 7 and 10 had AHIs > 30 events/h when diagnosed with OSA but lower values during this study. Because there were no crossover effects detected, time 2 of the CPAP-No CPAP group was aligned with time 4 of the No CPAP-CPAP group (after 2 weeks on CPAP therapy). These AHIs were compared to those at time 4 of the CPAP-No CPAP group aligned with time 2 of the No CPAP-CPAP group (after 2 weeks of no therapy).

Patient #	Gender	Age (y)	BMI (kg/m^2)	AHI (after 2 weeks with CPAP) events/h	AHI (after 2 weeks without CPAP) events/h
1	Female	35	43.34	17.4	1.4
2	Male	33	29.67	30.9	7.5
3	Male	40	44.72	39	5.5
4	Male	39	39.04	13	13.9
5	Male	44	35.45	74.9	17.7
6	Male	52	35.06	30.4	0.2
7	Male	63	30.77	27.9	2.3
8	Male	44	54.63	67.4	1.6
9	Male	42	30	28.2	1.4
10	Female	61	27.61	16.4	12.7
11	Female	51	32.84	30.4	4.9
12	Female	49	27.34	30	3.6
Mean ± SD		46 ± 9	36 ± 8	34 ± 19	6 ± 6

AHI data correspond to Time 2 (2 weeks without CPAP) and Time 4 (2 weeks with CPAP) in Fig. 1.

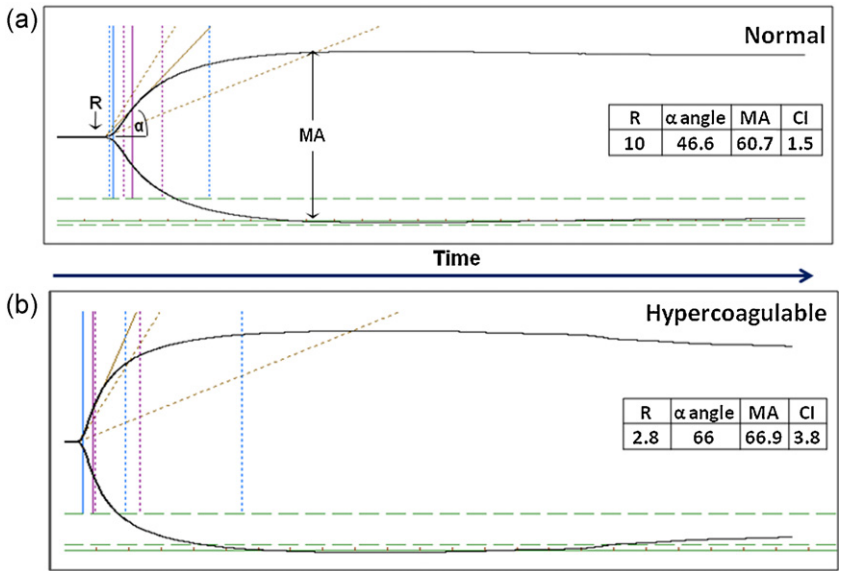

Fig. 2. Representative TEG traces demonstrating (a) normal trace with parameters of coagulation and fibrinolysis defined together with reference normal ranges for each parameter and (b) hypercoagulable traces from two of our patients. Hypercoagulability is indicated by one of more of the following: shortened *R* time, increased α angle, increased maximum amplitude (MA), and increased clot index (CI).

Table 2
Patients with severe OSA were hypercoagulable as assessed by TEG. Data reflect TEG values when patients were not on CPAP, referring to Times 1 and 2 in the No-CPAP/CPAP group and Times 1 and 4 in the CPAP/No-CPAP group.

TEG Parameter	*R* (min) Time to start initial fibrin threads	α (degrees) Speed of fibrin formation	MA (mm) Maximum strength of the clot	CI overall coagulation activity
Normal reference range	7–29	22–58	44–46	−3 to +3
Patients' average (NO CPAP)	7.2 ± 1.4	57.2 ± 9.1	68.2 ± 2.9	3.2 ± 0.6
Number of patients with abnormal values	10	6	12	9

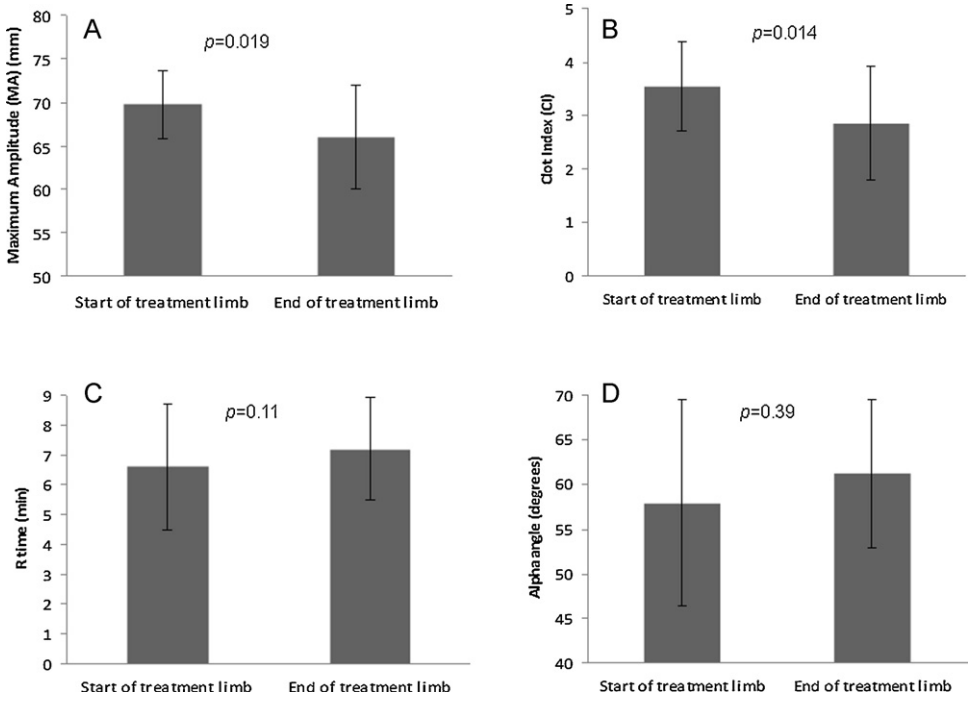

Fig. 3. The effect of CPAP on the haemostatic status in patients with severe OSA. CPAP significantly reduced MA and CI. *R* time was normalised, and there was no significant change in α angle.

of hypercoagulability did not correlate with the CPAP induced improvement of AHI. Finally, two weeks of CPAP treatment reduced this hypercoagulability based on reductions in MA and CI.

Several studies have documented hypercoagulability in OSA patients and some reported the effect of CPAP on coagulability; however, these studies have often investigated just one or more individual parameters of coagulation (for review, see Liak and Fitzpatrick, 2011). This is the first randomized, controlled, crossover study employing TEG with analysis of all parameters to assess hypercoagulability in patients with severe OSA. Each patient had at least one abnormal TEG parameter prior to CPAP, and which was subsequently improved by CPAP. To date, apart from a study using TEG in a rat model of the disease (Othman et al., 2010a), only one study has reported its use in patients with OSA (Guardiola et al., 2001). There are two major differences between our study and theirs. First, they compared coagulability in patients with OSA with that of "healthy" subjects and therefore did not, as they acknowledged, allow for confounding comorbidities that affect coagulability. In our study, the crossover design eliminated this problem because each patient served as his or her own control. Second, Guardiola and colleagues measured only the *R* time, reflecting a change in coagulation factors, and not the α angle and MA that assess other aspects of the haemostatic process, mainly those related to thrombin generation, fibrin build up and the quality of platelet function.

The basis for the hypercoagulability of OSA, particularly severe OSA, is unknown. However, the hypoxia associated with apnoea and hypopnoea is likely critical as it causes the expression of several factors that influence coagulation. Hypoxic endothelial cells are known to promote coagulation in two ways: (1) suppression of thrombomodulin, a membrane protein, thereby slowing the catalytic activation of protein C, an anticoagulant, by thrombin; and (2) increasing the expression of tissue factor, which initiates the extrinsic pathway of coagulation (Ten and Pinsky, 2002). Hypercoagulability is a leading cause for pathological thrombosis which would greatly increase morbidity and mortality in OSA patients (Cohen et al., 2010; Glacet-Bernard et al., 2010; Cistulli and Phillips, 2010; Leroux les Jardins et al., 2009). What remains unclear are the roles of the intermittent nature and severity of hypoxia on these responses in patients with OSA. In addition, there have been no studies of the contributions to hypercoagulability, if any, of the hypercapnia and the acute and chronic increases in sympathetic activity associated with OSA.

Despite all patients having severe OSA at the time of diagnosis, they exhibited varying levels of hypercoagulability as shown by TEG. For example, overall clotting activity (CI) before CPAP ranged from 2.7 to 4.0 (normal −3 to +3). The poor correlation in our study between TEG parameters and the severity of OSA (AHI) is not surprising given that multiple comorbidities associated with severe OSA also influence coagulability. A larger patient population needs to be tested in order to determine the contributions of the severity of sleep apnoea as well as other coexisting cardiovascular risk factors to thrombotic tendency.

One of the critical clinical issues in the management of OSA is poor adherence to CPAP treatment due to patient characteristics, technical devices and side effects (Galetke et al., 2011; Sawyer et al., 2011). Because patients with untreated OSA are at a significantly greater risk of cardiovascular complications, the question arises: would monitoring of coagulability help identify OSA patients at increased risk of cardiovascular events and thereby identify a group in whom adherence to treatment is critical? Alternatively, could measurements of coagulability in patients with OSA with poor adherence to treatment identify those who could benefit from anticoagulant treatment?.

The utility of TEG in OSA has not been systemically evaluated. Introduced in 1948, the use of TEG has been limited to monitoring liver transplantation, cardiac surgeries and intravenous infusions (Pivalizza and Abramson, 1995). Recent efforts in the standardization of the sampling procedures and techniques have expanded its application to include several haematological and non-haematological conditions (Chitlur et al., 2011; El Kady et al., 2009; MacDonald and Luddington, 2010; Othman et al., 2009, 2010b). TEG is a relatively simple test that provides information about the full spectrum of the complex haemostatic process, such as fibrin formation (reflecting thrombin generation), platelet count and function, levels of coagulation factors as well as the fibrinolytic component, compared to conventional tests that usually measure just one aspect of haemostasis such as PT, APTT, plasma fibrinogen, VWF levels and platelet aggregation. Furthermore, it requires a small sample volume (340 μL of blood). While we acknowledge the limited size of our study population, the significant changes we observed after just two weeks of CPAP indicates the potential value of TEG in assessing coagulability in patients with OSA. In addition, the fact that the beneficial effect of CPAP appears to be elicited within a short term treatment (2 weeks) indicates that correction of hypoxia may be a possible therapeutic mechanism and may explain why this effect is reversed after cessation of therapy.

5. Conclusion

Patients with severe OSA are, according to TEG, hypercoagulable and two weeks of CPAP reduces this hypercoagulability. These data suggest that a large scale study be undertaken to determine the extent of hypercoagulability in patients with OSA, the relation between OSA severity and hypercoagulability and, eventually, the role of anti-coagulants in patients with poor adherence to CPAP.

Conflict of interest

The authors have no conflict of interest.

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