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REVIEW

Vasomotion – what is currently thought?

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Abstract

This minireview discusses vasomotion, which is the oscillation in tone of blood vessels leading to flowmotion. We will briefly discuss the prevalence of vasomotion and its potential physiological and pathophysiological relevance. We will also discuss the models that have been suggested to explain how a coordinated oscillatory activity of the smooth muscle tone can occur and emphasize the role of the endothelium, the handling of intracellular Ca^{2+} and the role of smooth muscle cell ion conductances. It is concluded that vasomotion is likely to enhance tissue dialysis, although this concept still requires more experimental verification, and that an understanding at the molecular level for the pathways leading to vasomotion is beginning to emerge.

Keywords arteries, chloride conductance, smooth muscle.

Historical background

Vasomotion is the oscillation in tone of blood vessels, which gives rise to flowmotion, which is an oscillation of flow into an organ. This phenomenon was described by Jones more than 150-years ago based on studies of the bat wing circulation (Jones 1852) and has since been reported in many vascular beds from different species both *in vivo* and *in vitro*. In spite of the incidence of this phenomenon neither the mechanism causing blood vessels to oscillate in a coordinated manner nor the physiological and/or pathophysiological consequences are fully understood or agreed upon. In this short review, we will summarize the current views on the prevalence of vasomotion and the mechanisms for this coordinated activity of the smooth muscle cells in the vascular wall.

Prevalence of vasomotion

Flowmotion is a consequence of vasomotion

Vasomotion *in vivo* is associated with the rhythmic oscillations in vessel diameter (Slaaf *et al.* 1987, Meyer *et al.* 1988, Bouskela & Grampp 1992, Bouskela & Cyrino 1994, Verbeuren *et al.* 1997). These oscillations of the lumen diameter modify blood flow in a corresponding fashion and produce periodical fluctuations known as flowmotion (Schmidt 1996). Thus, flowmotion describes an oscillatory phenomenon, which is the result of vasomotion (Slaaf *et al.* 1988). Vasomotion has been termed 'a more local phenomenon' (Slaaf *et al.* 1988, Siegel *et al.* 1991) and can be observed *in vivo* only by intravital microscopy, a technique which is not always easily applicable to the study object (Kaufman & Intaglietta 1985). Flowmotion is, in contrast, easier to access through Laser-Doppler flow (LDF) measurements as well as some other methods, such as oxygen tension and local blood pressure measurements (Mahler *et al.* 1979, Bollinger *et al.* 1991, Tsai & Intaglietta 1993, Collin *et al.* 2000, Westermaier *et al.* 2009, Ances *et al.* 2010, Welsh *et al.* 2010). A problem with these measurements is that they are influenced by neighbouring vessels and central circulatory factors, such as blood pressure fluctuations (Slaaf *et al.* 1987, Kastrup *et al.* 1989, Weiss *et al.* 1992, Bollinger *et al.* 1993, Jamsek & Stefanovska 2007). Thus, measured flowmotion is not necessary a consequence of rhythmic activities in the blood vessels, where the flow is measured. Although *in vivo* flowmotion may represent an integration of several periodic activities of different origin (Stefanovska 2007), the results obtained with LDF measurements provide the majority of data on the prevalence of oscillations in the vascular wall *in vivo* (Schmidt 1996, Nilsson & Aalkjaer 2003, Rossi *et al.* 2006b).

Flowmotion in vivo contains a spectrum of frequencies

Analyses of flowmotion measured *in vivo* by LDF (Bollinger *et al.* 1991, Kvernmo *et al.* 1998, Kvandal *et al.* 2003, Bernjak *et al.* 2008, Bocchi *et al.* 2010, Welsh *et al.* 2010, Rossi *et al.* 2011), by measurements of oxygen tension (Thorn *et al.* 2009) as well as video recordings of blood cell velocity and capillary pressure measurements in the nailfold (Fagrell *et al.* 1977, Mahler *et al.* 1979) revealed a broad spectrum of oscillation frequencies (Stefanovska 2007). The observed frequencies have been classified into several groups, where high-frequency oscillations originating from the heart and respiratory movements are followed by several distinct bands of lower frequencies (Siegel *et al.* 1991). These lower frequencies were later shown to have different mechanistic backgrounds (Kvernmo *et al.* 1999). An analysis of the LDF measurements in the human skin reveals flowmotions in frequency bands between 0.0095 and 2 Hz (Kvernmo *et al.* 1998, Kvandal *et al.* 2006). Further, pharmacological intervention subdivided these frequencies into groups that are primarily dependent on the vascular endothelium, neurogenic activity and intrinsic smooth muscle activity (Stefanovska 2007). The myogenic-related flowmotion *in vivo* with frequencies of 0.05–0.2 Hz likely represents vasomotion seen in many isolated small arteries (Aalkjaer & Nilsson 2005).

Only few systematic studies have correlated vasomotion to the size of the arteries. This work has mostly been carried out by Colantuoni *et al.* who used the hamster skin-fold window preparation (Colantuoni *et al.* 1984c, 1985a,b, 1990). They found that the frequency of vasomotion is highest in the smallest arteries. Thus, terminal arterioles (<15 μm) have higher frequencies of oscillation compared with bigger ($\sim$100 μm) arterioles (Colantuoni *et al.* 1984c, 1985a,b, 1990). Also Oude Vrielink *et al.* (1990) found differences in vasomotion characteristics depending on the vessel size.

Vasomotion can be elicited in vitro

Vasomotion can be observed *in vitro* under various experimental conditions. Vasomotion has been recorded as oscillations in the wall tension under isometric conditions (Peng *et al.* 2001, Mauban & Wier 2004, Borovik *et al.* 2005, Hessellund *et al.* 2006, Matchkov *et al.* 2006, Boedtkjer *et al.* 2008, Koenigsberger *et al.* 2008) and as oscillations in the arterial diameter under isobaric conditions (Osol & Halpern 1988, Haddock *et al.* 2002, 2006, Oishi *et al.* 2002, Okazaki *et al.* 2003, Schuster *et al.* 2004, Rahman *et al.* 2005). In general, the frequencies observed *in vitro* correlate well with *in vivo* flowmotion of myogenic origin (Kvandal *et al.* 2006, Stefanovska 2007). Vasomotion with a frequency ranging from 0.01 to 0.3 Hz is seen in isolated arteries from various species – including humans – and in blood vessels from different sites in the body (Nilsson & Aalkjaer 2003). It has been suggested that vasomotion is seen more prominently in the small arteries than in the conduit arteries (Gustafsson 1993, Lamboley *et al.* 2003, Nilsson & Aalkjaer 2003, Haddock & Hill 2005, van Helden *et al.* 2006), although there are also reports documenting its presence in the carotid artery of rat (Masuda *et al.* 1982) and dog (Siegel 1983).

The appearance of vasomotion *in vitro* strongly supports the suggestion that the mechanism initiating vasomotion is inherent to the vascular wall (Peng *et al.* 2001). However, the complexity of oscillations *in vivo* indicates a multifaceted modulation through several extravascular mechanisms including neural influences (Schmidt 1996). Studies of vasomotion *in vitro* are essential to elucidate the cellular mechanism(s) responsible for vasomotion, whereas *in vivo* knowledge is essential to address the physiological significance of this phenomenon. Although vasomotion is eagerly studied under both *in vivo* and *in vitro* conditions, there is little interaction between the groups working with isolated blood vessels or *in situ* conditions. It is likely that significant improvement in our understanding of vasomotion could be obtained by more interactions between the two approaches used to investigate this phenomenon.

Experimental conditions affect the prevalence of vasomotion in vitro

Many experiments investigating vasomotion have been performed using anaesthetized animals. This has provoked an intense debate whether vasomotion is inhibited in anaesthetized animals or that metabolic and acid-base changes associated with anaesthesia stimulate vasomotion (Schmidt 1996, Nilsson & Aalkjaer 2003).

Several animal studies have reported the presence of vasomotion or the myogenic component of flowmotion under completely conscious condition and their disappearance in anaesthetized animals (Colantuoni *et al.* 1984a, Hundley *et al.* 1988, Wilkin 1989). In the hamster skin-fold preparation, vasomotion had been shown to be highly prevalent under control condition, but disappeared during anaesthesia (Colantuoni *et al.* 1984a). This effect was independent of anaesthesia type (Colantuoni *et al.* 1984a) and was consistent for skin (Colantuoni *et al.* 1984b, Wilkin 1989), brain (Hundley *et al.* 1988) and skeletal muscle (Slaaf *et al.* 1987) circulations of different species. These reports are in contrast to studies on the rabbit skeletal muscle circulation, which suggested a very low prevalence of

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vasomotion in this vascular bed under physiological conditions (Borgström *et al.* 1992, Schmidt *et al.* 1995, Schmidt-Lucke *et al.* 2002). There are also other reports on vasomotion and flowmotion during anaesthesia (Burrows & Johnson 1981). Schmidt (1996) in his comprehensive review of vasomotion expressed concern that most reports on vasomotion and flowmotion do not provide a sufficient description of the prevalence of oscillations, but are focusing on the experiments, where this phenomenon is present of e.g. in some studies a TA (transverse arteriole) was selected that clearly showed vasomotion (Oude Vrielink *et al.* 1990). This could potentially select for a subset of arteries although it is also stated in that article that 'vasomotion was a common observation along all TAs'. Further, Schmidt (1996) suggests that most of the reported vasomotion and flowmotion in experimental animals are consequences of changes in acid-base status (acidification) and reduced flow either due to less than perfectly controlled anaesthesia or pathological conditions. In his own studies, flowmotion was absent or had low prevalence if the anaesthesia was well-controlled (Borgström *et al.* 1992, Schmidt *et al.* 1995, Schmidt-Lucke *et al.* 2002). Importantly, though, vasomotion and the myogenic component of flowmotion have been identified in numerous human studies in the skin circulation with and without anaesthesia (Wilkin 1986, Bollinger *et al.* 1991, Kano *et al.* 1991).

What seems clear from the aforementioned factors and studies that the precise prevalence of vasomotion for any particular vascular bed under normal conditions can be difficult to ascertain. Of greater potential importance is to understand the association between different pathological states and the prevalence of vasomotion.

Many disease states are associated with changes in vasomotion

The prevalence of vasomotion in human is changed significantly depending on pathology and experimental conditions (Wilkin 1986, Kano *et al.* 1991, Bernardi *et al.* 1997, Collin *et al.* 2000, Lefrandt *et al.* 2003, Meyer *et al.* 2003a,b, 2009, Rossi *et al.* 2006a,b, 2009, 2011, Bocchi *et al.* 2010).

There is substantial evidence that diabetes both in humans (Benbow *et al.* 1995, Stansberry *et al.* 1996) and in experimental animal models (Bouskela 1988, Bouskela *et al.* 1997, Renaudin *et al.* 1999) is associated with an altered pattern and/or reduced prevalence of vasomotion. It is well established that vasomotion is under strong modulatory influence by sympathetic innervation (Kastrup *et al.* 1989) and it has been suggested that altered vasomotion in diabetes is due in part to the associated neuropathy (Rossi *et al.* 1990, Benbow *et al.* 1995, Lefrandt *et al.* 2003). This conclusion was supported by the observation that the vasomotion affected by diabetes has a frequency of 0.1 Hz (Bocchi *et al.* 2010), which is the frequency range associated with influence from the sympathetic nervous system and because the abnormality is predominantly seen in diabetic patients with neuropathy (Benbow *et al.* 1995). Reduced arterial vasomotion has even been suggested to be an early index of sympathetic dysfunction (Bernardi *et al.* 1997, Meyer *et al.* 2003a). The important role of the sympathetic innervation for vasomotion has been confirmed from *in vitro* experiments (Borovik *et al.* 2005), where it has been demonstrated that selective activation of the nerves in the vascular wall can reset the phase of vasomotion. This would suggest that *in vivo* a burst of sympathetic activity to a vascular bed can phase-lock various segments in the bed and thus be important for maintaining a synchronized activity throughout a vascular bed. This notion received direct experimental support in a study, where severe dysautonomia in diabetic neuropathy in type 2 diabetes was treated with frequency rhythmic electrical modulation system (FREMS) (Bocchi *et al.* 2010). Dysautonomia was correlated with the loss of 0.1 Hz vasomotor activity and impaired microcirculation. It was shown that FREMS was able to synchronize smooth cell activity, inducing and increasing 0.1 Hz vasomotion and thus improve microcirculation independently from the autonomic nervous system (Bocchi *et al.* 2010).

Several other factors are important for diabetes-associated disturbances of vasomotion. Thus, insufficient glycemic control has been shown to be a risk factor in the pathogenesis of impaired vasomotion in type 1 diabetes (Meyer *et al.* 2003b), although the significance of this mechanism has been questioned in a later study (Meyer *et al.* 2009). The importance of a metabolic component has been supported by the reduction of all types of vasomotion in obese patients, regardless of diabetes status and by the demonstration that sustained weight loss is able to fully normalize vasomotion in the skin (Rossi *et al.* 2011). Insulin infusion has also been shown to induce vasomotion with a frequency of about 0.1 Hz in a rat model of acute insulin resistance (Newman *et al.* 2009). The effect has been suggested to be through an effect of insulin on the endothelium and is of significance for the enhancement of capillary perfusion and glucose uptake in skeletal muscles (Clough & Egginton 2009, Newman *et al.* 2009, Wiernsperger & Bouskela 2009). Furthermore, it has been suggested that the impaired vasomotion in type 2 diabetes may favour the development of arterial hypertension (Meyer *et al.* 2003b).

Metabolic acidosis has been suggested to potentiate vasomotion in skeletal muscle circulation

(Schmidt-Lucke *et al.* 2002), whereas one report demonstrated the inhibition of vasomotion with respiratory acidosis in the cerebral circulation *in vivo* (Morita-Tsuzuki *et al.* 1992). *In vitro* both normo- and hypercapnic acidosis inhibited vasomotion (Peng *et al.* 1998a), whereas hypocapnia potentiated it (Morita-Tsuzuki *et al.* 1992, Peng *et al.* 1998b). Haemorrhage has also been demonstrated to increase the prevalence of vasomotion (Gustafsson *et al.* 1991, Vollmar *et al.* 1994). Interestingly, it has been suggested that anaesthesia could reduce the blood supply to tissues and thus mimic the effect of haemorrhage in inducing vasomotion (Schmidt 1996). Another important parameter, which changes during circulatory failure, is reduction in transmural pressure (Schmidt 1996). Vasomotion *in vitro* has been demonstrated to be most pronounced when the wall tension corresponds to the lower portion of the autoregulatory range (Osol & Halpern 1988). This suggests that vasomotion might be potentiated by a transmural pressure reduction to near the lower range of the autoregulatory range and that vasomotion will disappear when the transmural pressure falls below the autoregulatory region or is at the high end of this range. Finally, it is important to note that temperature is also a critical experimental parameter and vasomotion has been shown to disappear with heat stress (Ryan & Gisolfi 1995, Sakurai & Terui 2006). This is supported by earlier LDF measurement, which showed that flowmotion is suppressed at high temperatures (Pyykko *et al.* 1986, Kastrup *et al.* 1989).

Hypertension also alters the pattern of vasomotion. Although in the skin of humans with essential hypertension vasomotion seems identical, evidence has been provided for an impaired vasomotion following ischaemia in this group (Rossi *et al.* 2006a). Isolated arteries from skin biopsies of humans with hypertension have been extensively investigated (Aalkjaer *et al.* 1987, Thybo *et al.* 1995, Rizzoni *et al.* 1998), but it has been difficult to elicit vasomotion in these arteries under *in vitro* conditions. Therefore, it has not been possible to confirm the *in vivo* observations under *in vitro* conditions. Conversely, in isolated omental arteries from pregnant women with pre-eclampsia an increased prevalence of vasomotion has been reported (Aalkjaer *et al.* 1985). In animal models of hypertension, increased prevalence of vasomotion has consistently been reported (Osol & Halpern 1988, Lefer *et al.* 1990, Boegehold 1993, Zhang *et al.* 2000, Chen *et al.* 2010), which contrasts somewhat with the limited findings in humans.

Potential consequences of vasomotion

The altered prevalence or pattern of vasomotion under pathological conditions implicates vasomotion in several pathological conditions. However, it does not provide much insight into the physiological or pathophysiological role of vasomotion (Nilsson & Aalkjaer 2003). The observations that areas threatened by homoeostatic and metabolic stress have an enhanced pattern of vasomotion (Bertuglia *et al.* 1991, Schmidt *et al.* 1992) – although this is not universally reported (Slaaf *et al.* 1987) – together with theoretical considerations suggest that vasomotion is important for optimal blood flow and tissue dialysis (Ohta *et al.* 1988, Iida 1990, Bollinger *et al.* 1993, Tsai & Intaglietta 1993, Rucker *et al.* 2000, Goldman & Popel 2001).

The aforementioned high prevalence of vasomotion at the lower end of the autoregulatory pressure range (Osol & Halpern 1988, Schmidt *et al.* 1992, Ren *et al.* 1994) is consistent with vasomotion being important when the microcirculation is in a critical state (Schmidt 1996, Westermaier *et al.* 2009). It has been shown that in patients with mild peripheral arterial occlusive disease (PAOD) the prevalence of vasomotion is increased. Of specific interest is the observation that when these patients were divided into those exhibiting flowmotion and those who did not, those with flowmotion had significantly higher tissue oxygen levels than those patients without, despite similar blood flow (Schmidt *et al.* 1993, Schmidt 1996). This is in accordance with other studies on PAOD patients (Scheffler & Rieger 1992, Hoffmann *et al.* 1994) and the prevalence of vasomotion in patients after compression therapy (Pekanmaki *et al.* 1991). Mathematical modelling supports the importance of vasomotion for oxygen delivery (Ohta *et al.* 1988, Tsai & Intaglietta 1993, Goldman & Popel 2001, Pradhan & Chakravarthy 2007, Hapuarachchi *et al.* 2010) and suggests that its activity can change oxygen delivery to tissues by up to eightfold (Kislukhin 2010) although more recent analysis indicates a more complex role of vasomotion. In one study (Goldman & Popel 2001), vasomotion only enhanced oxygen delivery in the skeletal muscle bed when myoglobin was low. In another modelling approach, where the physical movement of the arteriolar wall was included in the model, less oxygen delivery by the arterioles exhibiting vasomotion was found and it was suggested that this might lead to high oxygen tension and possibly enhanced delivery by the capillaries (Hapuarachchi *et al.* 2010). The authors of this article concluded as do we that the effect of vasomotion on transport of oxygen to tissue 'is highly complicated'. The limited experimental evidence does, however, indicate an importance of flowmotion for tissue oxygen tension. Optimal tissue oxygen tension in cat retina has been shown to be dependent on arteriolar vasomotion and fluctuations in the capillary perfusion (Braun *et al.* 1992). Furthermore, in rabbits hemodilution and local blood pressure reduction induced myogenic flowmotion

in the skeletal muscle vasculature, which could be prevented with the Ca^{2+} channel antagonist diltiazem (Schmidt 1996). Although only limited experimental details were provided, it appears that the experiments were designed to maintain the same flow in the diltiazem (without vasomotion) and control (with vasomotion) group. It was concluded that vasomotion in a situation of critical ischaemia increases aerobic tissue metabolism. Another interesting report (Sakurai & Terui 2006) addressed this question by modifying sympathetically driven vasomotion *via* temperature changes and observing the clearance of a tracer from the interstitial compartment. The data indicated a clear enhancing effect of vasomotion on the clearance of tracer (Fig. 1) for the same mean blood flow, providing direct support for a role for vasomotion in the effective dialysis of tissues. Along the same lines the importance of vasomotion for tissue metabolism is provided from studies in testis, where vasomotion is essential for the normal function (Widmark *et al.* 1986, 1989, Damber *et al.* 1990, Welsh *et al.* 2010). An inhibition of vasomotion in testis by hormonal disturbances or increase in temperature does not affect the mean blood flow, but is associated with impaired interstitial fluid dynamics and formation and reduced oxygen and nutrient exchange over the capillary wall (Widmark *et al.* 1986, 1989, Damber *et al.* 1992, Setchell *et al.* 1995, Collin *et al.* 2000, Lysiak *et al.* 2000, Welsh *et al.* 2010). Such changes have been shown to significantly suppress and finally abolish key testicular functions. Also in the foot skin from diabetic patients it has been shown that reduced vasomotion is associated with decrease in effective dialyses of the tissue and an abnormal capillary leakage (Lefrandt *et al.* 2003) and as discussed above, in patients with peripheral occlusive artery disease vasomotion also appears to promote tissue oxygenation (Schmidt 1996).

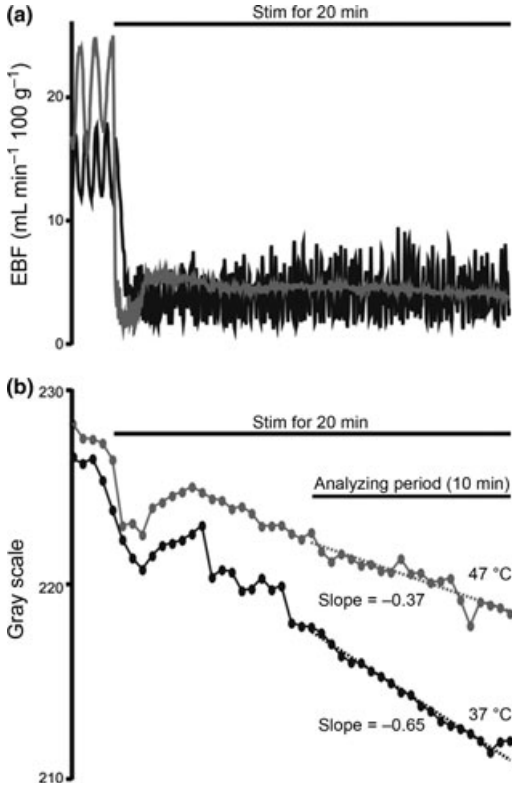

Figure 1 Vasomotion is important for tissue-capillary fluid exchange. The washout of Cr-EDTA injected into the rabbit ear (b) was dependent on the presence of vasomotion (black in a and b) – being faster when vasomotion was present. This strongly suggests an importance of vasomotion for efficient tissue perfusion. (From Sakurai & Terui 2006).

Thus, there is no doubt that a better understanding of the mechanism underlying vasomotion will improve our knowledge of its physiological significance, but the opposite may also hold true, that is to say an altered prevalence of vasomotion under certain pathophysiological conditions may provide clues for mechanistic insight, e.g. an association between changes in TRPC channel expression in experimental hypertension and increased prevalence of vasomotion has been recently suggested (Chen *et al.* 2010).

Mechanism(s) of vasomotion

To get closer to the role of vasomotion one strategy would be to identify the key cellular mechanisms important to vasomotion. With this knowledge, it would be possible to specifically interfere with one or more of these essential mechanisms essential and subsequently address vasomotion's physiological importance.

Vasomotion is a product of multiple intracellular and intercellular systems, which seemingly interact with each other in variable combinations. Thus, the inhibition of one oscillatory component in the vascular wall may not necessary eliminate vasomotion totally, but may indeed unmask another oscillator and enable vasomotion, albeit with differing characteristics than before (Rahman *et al.* 2007, Boedtkjer *et al.* 2008). Observations, such as these may explain why the mechanism of vasomotion varies between different species and between different vascular beds within the same species.

Intracellular Ca^{2+} transients – Ca^{2+} waves represent the activity of a cytosolic oscillator

For the generation of vasomotion the presence of a cellular oscillator or oscillators is necessary (Berridge & Rapp 1979, Aalkjaer & Nilsson 2005). Based on their mechanism, cellular oscillations can be divided into

cytosolic and membrane oscillators (Nilsson & Aalkjaer 2003, Haddock & Hill 2005). An oscillator, which originates from the cytoplasm may not necessarily be coupled to membrane potential changes (Miriel *et al.* 1999, Haddock & Hill 2002), but depends on release of Ca^{2+} from intracellular Ca^{2+} stores, for example, the sarcoplasmic reticulum (SR). An intracellular oscillator can normally be visualized under experimental conditions in form of intracellular Ca^{2+} ($[Ca^{2+}]_i$) transients, which spread from one part of the cell to another (Peng *et al.* 2001, Jacobsen *et al.* 2008). This gives the appearance of Ca^{2+} waves (Fig. 2). These periodic events are not synchronized between neighbouring cells and an asynchronous Ca^{2+} wave activity can be observed in individual vascular smooth muscle cells (VSMC) even under resting conditions (Bova *et al.* 1990, Iino *et al.* 1994, Miriel *et al.* 1999, Ruehlmann *et al.* 2000, Peng *et al.* 2001). The Ca^{2+} waves can appear in response to stimulation by agonists producing IP_3 consequent to Ca^{2+} release from the SR, which propagates along the cytoplasm (Rahman *et al.* 2005, Jacobsen *et al.* 2008). The Ca^{2+} waves may also appear spontaneously (Ruehlmann *et al.* 2000, Zang *et al.* 2001) and are often more prevalent when low concentrations of contractile agonists are applied (Jaggar & Nelson 2000, Lee *et al.* 2001, Peng *et al.* 2001, Sell *et al.* 2002, Lamboley *et al.* 2003, Rahman *et al.* 2005). The Ca^{2+} waves initiated in VSMC by agonist stimulation do not represent simple diffusion of Ca^{2+}, but require regeneration by Ca^{2+}-induced Ca^{2+} release from the SR, which allows $[Ca^{2+}]_i$ transients to propagate over substantial distance without decrement in amplitude (Iino *et al.* 1994, McCarron *et al.* 2004). Both IP_3- and ryanodine-sensitive channels are potentially important and their role is experimentally verified (Iino *et al.* 1994, Miriel *et al.* 1999, Lee *et al.* 2001, Peng *et al.* 2001). The Ca^{2+} waves show a considerable heterogeneity between different smooth muscle cells in the arterial wall (Peng *et al.* 2001, Rahman *et al.* 2005, Jacobsen *et al.* 2008). When $[Ca^{2+}]_i$ is integrated over an entire cell with time, these Ca^{2+} waves appear as rhythmical oscillation in $[Ca^{2+}]_i$, but their asynchrony will not lead to oscillations in tension. Oscillations in tension (vasomotion) appear when $[Ca^{2+}]_i$ oscillations in VSMC become synchronized. When this happens Ca^{2+} waves disappear and global oscillations in $[Ca^{2+}]_i$ are observed (Fig. 2), that is, a uniform rise in $[Ca^{2+}]_i$ throughout the cell occurs (Mauban *et al.* 2001, Peng *et al.* 2001, Sell *et al.* 2002, Lamboley *et al.* 2003, Jacobsen *et al.* 2008).

A membrane oscillator is essential for intercellular synchronization in the vascular wall

In the majority of reported cases, with one exception (Hill *et al.* 1999, Haddock *et al.* 2002), vasomotion has been reported to be voltage-dependent in the sense that oscillations in membrane potential are associated with the vasomotion (Segal & Beny 1992, Gustafsson 1993,

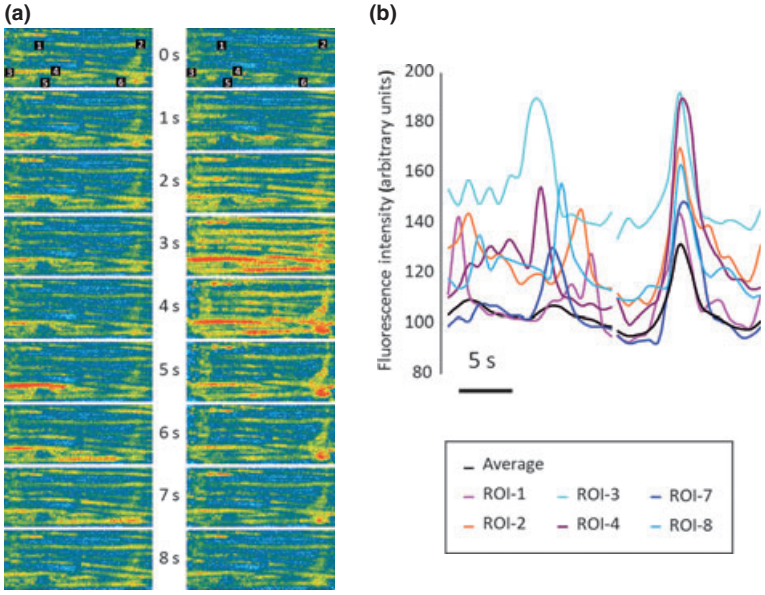

Figure 2 Asynchronous $[Ca^{2+}]_i$ waves (*left panel*) and synchronized $[Ca^{2+}]_i$ oscillations (*Right panel*) in mesenteric small artery loaded with calcium green/AM as described previously (150). An arterial segment was mounted in a isometric myograph and stimulated with $6{\cdot}10^{-6}$ M noradrenaline. Initially, asynchronous $[Ca^{2+}]_i$ waves appeared (*left panel*). The global $[Ca^{2+}]_i$ oscillations (*right panel*) appeared after a delay and represented a synchronous increase of $[Ca^{2+}]_i$ in the entire cell. (a) Sequences of confocal images of $[Ca^{2+}]_i$ over time in smooth muscle cells. The first frame shows the regions of interest (ROIs) used in all frames for analysis, (b) Plot of intensities vs. time of selected cells in panel (a), ROIs and the average of the entire frame.

Gokina *et al.* 1996, Bartlett *et al.* 2000, Peng *et al.* 2001, Oishi *et al.* 2002, Matchkov *et al.* 2004b, 2006, Aalkjaer & Nilsson 2005). This voltage-dependency is a prerequisite for the global $[Ca^{2+}]_i$ oscillations in the synchronized VSMC (Aalkjaer & Nilsson 2005), where periodic depolarizations induce the periodic influx of Ca^{2+} *via* voltage-dependent Ca^{2+} channels (VDCCs). This type of synchronization is likely to arise from an interplay between cytosolic and membrane oscillators (Matchkov 2010). In this model, oscillations in membrane potential are caused by periodic activation of a depolarizing current (the membrane oscillator) that is stimulated by $[Ca^{2+}]_i$ being released in an oscillating manner from the SR (the cytosolic oscillator) (Jacobsen *et al.* 2007a,b). The depolarizing current will entrain smooth muscle cells by running through intercellular contacts – gap junctions – and lead to simultaneous opening of VDCCs and Ca^{2+} influx in neighbouring cells. This synchronized Ca^{2+} influx increases the likelihood for synchronized Ca^{2+}-induced Ca^{2+} release, which further amplifies the depolarization and enables entrainment.

Due to the global character of membrane depolarization, Ca^{2+} influx through the VDCCs will occur simultaneously over the whole cell membrane. Thus, global Ca^{2+} changes (in contrast to Ca^{2+} waves) appear. Although significant discrepancies have been reported, this model (Fig. 3) provides a suitable explanation of the majority of reports on vasomotion in rat mesenteric arteries (VanBavel *et al.* 1991, Gustafsson 1993, Gustafsson & Nilsson 1993, 1994, Gustafsson *et al.* 1994, Tsai *et al.* 1995, Miriel *et al.* 1999, Peng *et al.* 2001, Schuster *et al.* 2001, 2004, Oishi *et al.* 2002, Sell *et al.* 2002, Lamboley *et al.* 2003, Rahman *et al.* 2005, Boedtkjer *et al.* 2008). In this model of vasomotion, the Ca^{2+} waves function as pacemakers for the global Ca^{2+} oscillations and, thus, vasomotion. In further support for the role of the membrane potential, the pharmacological blockade of VDCCs, immersion into a Ca^{2+}-free solution and hyperpolarization with an ATP-dependent K^+ channel opener all stop vasomotion in the rat mesenteric arteries and, as expected, transform the global Ca^{2+} oscillation to asynchronous Ca^{2+} waves (Peng *et al.* 2001, Jacobsen *et al.* 2008).

The Ca^{2+}-activated conductances initiate membrane potential oscillations

Several types of Ca^{2+}-activated membrane conductances, for example, Ca^{2+}-activated Cl^- channels, Ca^{2+}-activated K^+ channels and VDCCs can constitute membrane oscillators consequent to their activation by $[Ca^{2+}]_i$ and voltage (Salter *et al.* 1995, Bakhramov *et al.* 1996, Salter & Kozlowski 1998, ZhuGe *et al.* 1998, Smani *et al.* 2001, Cheong *et al.* 2002, Greenwood & Leblanc 2007). The Ca^{2+}-activated Cl^- channels have been suggested to be important for Ca^{2+}-induced depolarization in VSMC (Desilets *et al.* 1989, Salter *et al.* 1995, Bakhramov *et al.* 1996, Jensen *et al.* 1997, Lamb & Barna 1998, Hirakawa *et al.* 1999, Greenwood *et al.* 2001, Smani *et al.* 2001). We hypothesized that these channels might also be responsible for the

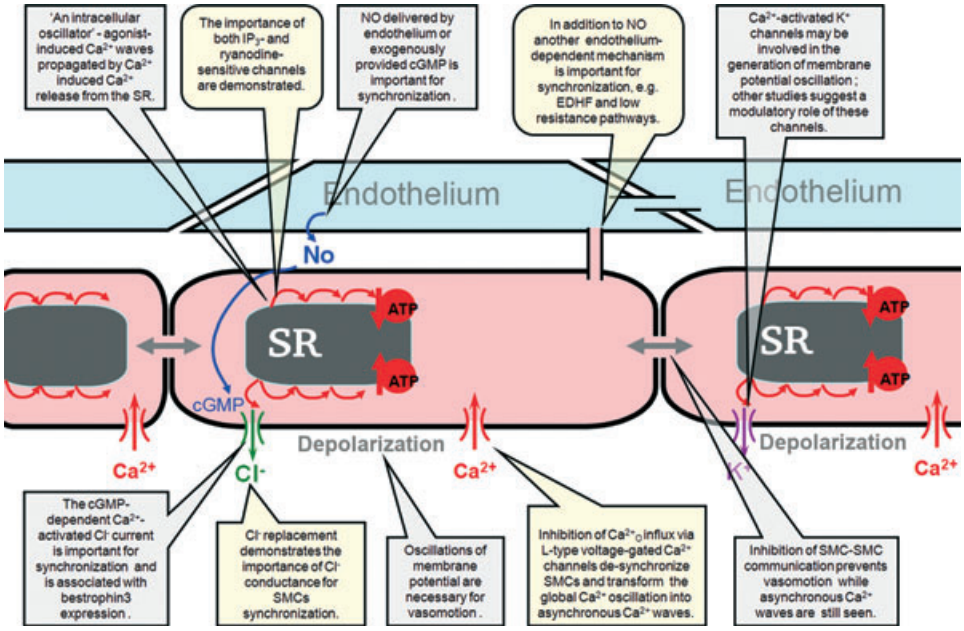

Figure 3 The key elements, which are important for vasomotion in rat mesenteric small arteries *in vitro*.

depolarizing phase of membrane potential oscillations (Peng *et al.* 2001, Matchkov *et al.* 2004a, Jacobsen *et al.* 2007b). Pharmacological interventions and anion substitution have demonstrated the importance of Ca^{2+}-activated Cl^- conductance for the generation of vasomotion (Boedtkjer *et al.* 2008).

The Ca^{2+}-sensitive K^+ channels could be responsible for the hyperpolarizing part of oscillations. Because of their slow activation kinetics, strong voltage-dependence and low sensitivity to $[Ca^{2+}]_i$ these channels will be substantially activated when the membrane depolarizes and $[Ca^{2+}]_i$ is significantly elevated (Brayden 1996, Gordienko *et al.* 1999, Jackson 2005, Thorneloe & Nelson 2005, Ledoux *et al.* 2006). Inhibition of K^+ membrane conductance in hamster cheek pouch arteries abolishes vasomotion and supports a role of K^+ channels (Bartlett *et al.* 2000). However, K^+ channel blockers have often been shown to modulate rat mesenteric artery vasomotion (Gustafsson & Nilsson 1994, Peng *et al.* 2001) suggesting that several different types of channels are involved in the repolarization phase.

The involvement of K^+ and Cl^- channels is not mandatory and several other membrane transporters have been suggested to act as membrane oscillators, for example, TRP channels (Beech 2005, Chen *et al.* 2010). According to some models, the repolarization may occur without the activation of a hyperpolarizing current, but be a consequence of refractoriness of the Ca^{2+}-release channels (McCarron *et al.* 2004) and consequent inhibition of the Cl^- channel. The Ca^{2+} release could also be slowed by depletion of the SR (Lee *et al.* 2001).

Vascular smooth muscle cells synchronize via intercellular channels – gap junctions

The synchronizing depolarization is suggested to pass through gap junctions in the form of an electrical signal. The arterial wall is equipped with low resistance channels, that is, gap junctions, which mediate this electrical coupling (Segal & Duling 1989, Bartlett *et al.* 2000, Emerson & Segal 2000, Sandow *et al.* 2003, Rummery & Hill 2004, Figueroa *et al.* 2006, Herve *et al.* 2007). Gap junctions consist of two hemichannels, which are aggregates of six transmembrane connexin proteins that dock to each other forming a channel between the adjacent cells (Brink 1998). At least four types of connexins (Cx37, 40, 43 and 45) have been identified in the vasculature (Matchkov *et al.* 2006, de Wit *et al.* 2006, Schmidt *et al.* 2008) and their distribution varies through the circulation and between different cell types (Brink 1998, Hill *et al.* 2002, Gustafsson *et al.* 2003). There is evidence for signalling *via* homocellular coupling (VSMC to VSMC, or endothelial to endothelial) and *via* heterocellular coupling (between smooth muscle and endothelial cells) in the vascular wall (Isakson & Duling 2005, Figueroa *et al.* 2006, de Wit *et al.* 2006). The exact role for each of the pathways for synchronization remains unknown. The observation that vasomotion in mesenteric small arteries can be recovered after mechanical removal of endothelium suggests a major role of homocellular coupling between smooth muscle cells for vascular wall synchronization (Peng *et al.* 2001, Boedtkjer *et al.* 2008). This 'recovered' vasomotion is, however, synchronized to a lesser extent than the intact arteries, which suggests that endothelium might play a supporting role (Peng *et al.* 2001, Rahman *et al.* 2005, Boedtkjer *et al.* 2008, Jacobsen *et al.* 2008).

The importance of gap junction in electrical synchronization of smooth muscle cells has received experimental support from the use of gap junction blockers. Interruption of gap junctions desynchronizes Ca^{2+} transients and membrane potential oscillations and stops vasomotion, but is without effect on Ca^{2+} waves (Tsai *et al.* 1995, Chaytor *et al.* 1997, Matchkov *et al.* 2004b, 2006, 2007). The nature of this signal, which spreads through the gap junctions, is debatable. Both electrical current (Peng *et al.* 2001, Jacobsen *et al.* 2007a,b) and Ca^{2+} (Koenigsberger *et al.* 2004) have been suggested as transmitters. As the Ca^{2+} waves in one cell have not been shown under experimental conditions to initiate Ca^{2+} waves in neighbouring cells, the movement of Ca^{2+} through gap junctions seems to be insignificant (Ruehlmann *et al.* 2000, Peng *et al.* 2001, Sell *et al.* 2002, Jacobsen *et al.* 2008). This could be because of limited number of gap junctions, a low concentration gradient for Ca^{2+} or due to a high buffering capacity of the cytosol. Therefore, the electrical current is most likely a candidate to substantially affect the membrane potential and induce Ca^{2+} influx through the VDCCs (Peng *et al.* 2001, Jacobsen *et al.* 2007a,b).

The role of endothelium

Vasomotion has been shown in many studies of isolated arteries to be endothelium dependent and several reports support that endothelial removal prevents vasomotion (Jackson 1988, Akata *et al.* 1995, Peng *et al.* 2001, Sell *et al.* 2002, Rahman *et al.* 2005, Boedtkjer *et al.* 2008). Several endothelium-derived factors have been suggested to be important for vasomotion, but the observation that a membrane-permeable analogue of cGMP could recover oscillatory behaviour suggested a major role for the NO system (Jackson *et al.* 1991, Gustafsson *et al.* 1993). Another important conclusion from these observations is that rhythmicity does not originate in the endothelium, but that a sustained concentration of endothelium-derived

NO/cGMP has a permissive role for smooth muscle cell synchronization. Consistent with this, the transition of asynchronous Ca^{2+} waves to synchronized Ca^{2+} oscillations in the rat mesenteric small arteries is prevented by endothelium removal (Peng *et al.* 2001) and synchronization of the Ca^{2+} oscillations can be obtained with a high concentration of cGMP (Peng *et al.* 2001, Rahman *et al.* 2005, Boedtkjer *et al.* 2008). This synchronization in the endothelium-denuded arteries treated with cGMP is not as complete as when the endothelium is present. The latter suggests that the endothelium provide a low resistance pathway (Yamamoto *et al.* 2001, Jacobsen *et al.* 2008) or other endothelium-derived factors in addition to NO may be important, for example the endothelium-derived hyperpolarizing factor (Mauban & Wier 2004).

The importance of the endothelium has been demonstrated in studies *in vitro* (Akata *et al.* 1995, Peng *et al.* 2001, Sell *et al.* 2002, Rahman *et al.* 2005, Boedtkjer *et al.* 2008) and *in vivo* (Kvernmo *et al.* 1999, Kvandal *et al.* 2003). In contrast, other studies in rabbit mesenteric and ear arteries, aorta and hamster cheek pouch, rat mesenteric and cerebral arteries demonstrated potentiating of vasomotion by endothelium removal or inhibition of NO production (Omote *et al.* 1992, Boegehold 1993, Dirnagl *et al.* 1993, Griffith & Edwards 1993b, Omote & Mizusawa 1993, Marchenko & Sage 1994, Bertuglia *et al.* 1995, Lacza *et al.* 2001). These inconsistencies could be because of the involvement of several endothelium-derived factors and their different prevalence in the different types of blood vessels under different experimental conditions (Schmidt 1996). It may also be relevant that the NO/cGMP pathway has several cellular targets, which are potentially important for generation of oscillations, that is, Ca^{2+} release from the SR is inhibited by cGMP (Rahman *et al.* 2005). The cGMP-dependent phosphorylation affects intercellular communications directly, but in a complex manner. Phosphorylation of connexins 37 and 43 inhibits intercellular communication (de Wit *et al.* 2006), whereas phosphorylation of connexin 40 seems to inhibit intercellular communication (Hoffmann *et al.* 2003, Kameritsch *et al.* 2003). Thus, depending on the incidence and type of gap junctions present in the arterial wall the effect of cGMP on intercellular communication can differ. The contrasting actions of cGMP suggest a complex role of cGMP in vasomotion and that the balance of its effects may define the role of the endothelium for vasomotion.

The model for generation of vasomotion in rat mesenteric small arteries

Several models for the generation of vasomotion have been suggested and have received experimental support (Griffith & Edwards 1993a, 1995, Griffith 1996, Lamboley *et al.* 2003, Nilsson & Aalkjaer 2003, Aalkjaer & Nilsson 2005, Haddock & Hill 2005, Jacobsen *et al.* 2007a,b, 2008, Parthimos *et al.* 2007, Koenigsberger *et al.* 2008). Although theoretical modelling cannot reproduce the pattern of vasomotion in all details, it can provide important insight into the major components relevant to vasomotion (Jacobsen *et al.* 2007a,b). The extensive studies of vasomotion in the rat mesenteric small arteries have made it possible to create a detailed model for the initiation of endothelium-dependent vasomotion in this vessel (Peng *et al.* 2001, Jacobsen *et al.* 2007a,b, 2008). This model (Fig. 3) suggests that agonist stimulation of smooth muscle cells induces intermittent release of Ca^{2+} from the SR, which activates a Ca^{2+}-dependent depolarizing conductance in the membrane when endothelium/cGMP is present (Peng *et al.* 2001, Rahman *et al.* 2005). Whereas this may occur randomly in different smooth muscle cells, the individual cells become synchronized by depolarization, which entrains Ca^{2+} transients in the individual cells (Jacobsen *et al.* 2007a,b). Thus, our model contains cytosolic oscillators represented by $[Ca^{2+}]_i$ waves in the individual smooth muscle cells and a synchronizing membrane oscillator, which is based on a cGMP dependent, Ca^{2+}-activated depolarizing current in the membrane of smooth muscle cells (Peng *et al.* 2001, Jacobsen *et al.* 2007a,b) (Fig. 3).

Cl^- conductance is essential for vasomotion in rat mesenteric small arteries

Previously, we have demonstrated the presence of two Ca^{2+}-activated Cl^- conductances in smooth muscle cells from mesenteric small arteries (Matchkov *et al.* 2004a, 2005, 2008). One of the Cl^- conductances exhibits the classical characteristics for the Ca^{2+}-activated Cl^- channels, whereas the other current has unique biophysical properties and cGMP is obligatory for its activation (Matchkov *et al.* 2004a, 2008, Piper & Large 2004a,b). On this background, we suggested that the oscillating Ca^{2+} activates a cGMP-dependent, Ca^{2+}-activated Cl^- current over the cell membrane (Matchkov *et al.* 2004a, 2005, 2008) to induce depolarization and consequently entrain the cells, as discussed above. To test this possibility, it was relevant to inhibit this current. However, the pharmacological tools available to block Ca^{2+}-activated Cl^- current are limited and rather unspecific (Greenwood & Leblanc 2007). Substitution of Cl^- with impermeable anions abolishes vasomotion in rat mesenteric small arteries, consistent with a critical role of Cl^- channels for the synchronized oscillations in the vascular wall: the changes in Cl^- transmembrane gradient have been shown to abolish vasomotion by stopping oscillations in membrane potential and desynchronizing $[Ca^{2+}]_i$ oscillation

(Boedtkjer *et al.* 2008). Although blockers with some specificity for Cl^- conductance in patch clamp experiments are available they are often not applicable for studying intact arteries because they under those conditions are unspecific (Matchkov *et al.* 2004a, Boedtkjer *et al.* 2008). Surprisingly, inhibition of one or both types of the Ca^{2+}-activated Cl^- currents by DIDS and Zn^{2+} did not stop vasomotion, but the vasomotion changed properties and became endothelium independent in the presence of these blockers (Boedtkjer *et al.* 2008). This endothelium-independent vasomotion was still inhibited by anion substitution suggesting an importance of a Cl^- conductance without permitting further definition of its type (Boedtkjer *et al.* 2008).

One of the ways to distinguish between the two Ca^{2+}-activated Cl^- conductances is a specific removal of the channel responsible for the current from cell membrane *in situ* (Hartzell *et al.* 2005). But this requires that the channels are known. Previously, we reported that siRNA-induced downregulation of bestrophin-3 in mesenteric small arteries *in vivo* was accompanied with significant inhibition of the cGMP dependent, Ca^{2+}-activated Cl^- current (Matchkov *et al.* 2008). It is very interesting that downregulation of bestrophin-3 also markedly reduced vasomotion in these arteries (Broegger *et al.* 2011). This finding lends strong support to the role of the Ca^{2+}-activated Cl^- current for vasomotion. Recently, the transmembrane protein TMEM16A/anoctamin-1 has been suggested to mediate Ca^{2+}-activated Cl^- currents (Caputo *et al.* 2008, Schroeder *et al.* 2008, Yang *et al.* 2008) and it will be of interest to evaluate the importance of this protein for Ca^{2+}-activated Cl^- currents in VSMC and for vasomotion. It is hoped that this molecular dissection of parameters important for vasomotion will eventually make it possible to modify *in vivo* cellular pathways and in this way generate tools that will further our understanding of the physiological and pathophysiological importance of vasomotion.

Other models for the generation of vasomotion

As discussed above, the two elements essential for vasomotion are the oscillator – which we believe is present in every cell and dependent on release of Ca^{2+} from the SR – and the synchronizing mechanisms, which we believe is the membrane potential (Peng *et al.* 2001, Jacobsen *et al.* 2007b). The model, we have suggested for mesenteric small arteries can also be applied to vasomotion in other vascular beds although some modification may be necessary (Fig. 2). The modification may include the significance and direction of endothelial involvement possibly consequent to the complex effects of cGMP in smooth muscle cells and also the importance of certain ion transporters, which may be differently expressed in different vascular beds (Matchkov 2010). Importantly, vasomotion was shown to be associated with oscillations in membrane potential in all vessels, where it has been measured (Mulvany *et al.* 1982, Garland 1989, Segal & Beny 1992, Gustafsson 1993, von der Weid & Beny 1993, Gokina *et al.* 1996, Peng *et al.* 2001, Haddock & Hill 2002, Oishi *et al.* 2002, Matchkov *et al.* 2004b) with the exception of irideal arterioles (Hill *et al.* 1999, Haddock *et al.* 2002). In mesenteric small arteries and in most other blood vessels, the voltage dependence of vasomotion is based on voltage-dependent Ca^{2+} influx, which is important for entraining individual oscillators (Peng *et al.* 2001, Jacobsen *et al.* 2007b). It is also possible that membrane potential oscillations could be a product of different membrane conductances with different $[Ca^{2+}]_i$ sensitivities or time-characteristics, for example, Ca^{2+}-activated Cl^- channels and Ca^{2+}-dependent K^+ channels (Salter *et al.* 1995, Bakhramov *et al.* 1996, Salter & Kozlowski 1998, ZhuGe *et al.* 1998, Smani *et al.* 2001). The generation of Ca^{2+} waves may also be generated through different pathways. The functional IP_3 receptors are essential for Ca^{2+} wave generation in rabbit inferior vena cava (Lee *et al.* 2001), in cultured aortic SMCs (Blatter & Wier 1992) and in rat portal vein (Boittin *et al.* 1999), whereas ryanodine receptor blockade will stop Ca^{2+} oscillations in rat mesenteric artery (Peng *et al.* 2001), in cultured aortic SMCs (Blatter & Wier 1992), in rat tail artery (Iino *et al.* 1994) and in rabbit inferior vena cava (Ruehlmann *et al.* 2000). There is also possibility that the two pathways are both involved and interact as it has been shown for the rat tail artery, where chronic downregulation of ryanodine receptors does not affect Ca^{2+} waves, probably because other Ca^{2+} release mechanisms take over (Dreja *et al.* 2001).

Conclusion

Vasomotion is observed in many vascular beds and is possibly present in all, but its quality and prevalence differs between vascular beds under normal conditions – thus there is still strong debate as to how prevalent vasomotion is under normal conditions. There is ample evidence to support that the prevalence of vasomotion is altered under pathological conditions. In particular, there is strong evidence that vasomotion prevalence increases in condition, where the blood supply to an organ is threatened. Modelling efforts suggest that, for a constant blood flow, vasomotion might be important for efficient delivery of nutrients to the tissue and washout of waste products, although the more recent modelling efforts suggest a very complex relationship between vasomotion and tissue dialysis. Only a handful of experiments has directly addressed this important question and there is further need for experimental

verification of the effect of vasomotion on tissue metabolism. Such experiments would be significantly aided if the mechanisms leading to vasomotion were fully understood at the cellular level. Models describing the cellular mechanisms involved are available although the caveat exists that the mechanism(s) may vary between different vascular beds. A common element appear to be Ca^{2+} release from the SR, which through activation of ion channels in the sarcolemma induces oscillations in the membrane potential thereby entraining smooth muscle cells and enabling the synchronicity necessary for vasomotion. Interestingly, one of the predictions from the models is the importance of a smooth muscle cell membrane Cl^- conductance and currently the importance for vasomotion of molecular candidates for this conductance are being tested experimentally.

Conflict of interest

The authors report no conflicts of interests.

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