The Filling Mechanism

6

Marcus Stoodley

Contents

6.1 Introduction

Syringomyelia is one of the most enigmatic conditions affecting the central nervous system. The seemingly simple nature of these intramedullary cysts belies the complexity that meets any serious investigation of the filling mechanisms. The pathophysiology may at first appear tantalizingly simple, yet closer inspection reveals complexity, and a satisfactory explanation remains elusive.

A myriad of theories have been proposed. Hydrodynamic theories generally assume that syrinx fluid is cerebrospinal fluid (CSF) that has entered the cord as a result of perturbations of pulsations in the subarachnoid space, caused by an associated Chiari malformation, arachnoiditis, or other abnormalities obstructing the subarachnoid space. Other theories propose that the fluid is not CSF, being formed predominantly from interstitial fluid. Suggested mechanisms include cord tethering, stretching the cord apart, and the Venturi effect in the subarachnoid space, expanding the cord by suction. Recent theories have proposed that disruptions of the blood-spinal cord barrier or alterations of aquaporin expression or function may result in excess fluid accumulation in the cord. Despite the plethora of theories, the pathophysiology of syringomyelia remains perplexing.

At a fundamental level, the volume of fluid and pressure in a syrinx are determined by the flow of fluid into and out of the cavity. A syrinx can only enlarge if net inflow exceeds net

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outflow; enlargement may therefore occur due to either increased inflow or decreased outflow. In addition to such factors, there may be local tissue characteristics that limit or permit syrinx expansion and influence internal pressure and the effect that it has on cord neurological function.

Syringomyelia is associated with many conditions, and the filling mechanism may, of course, be different in each case. Whether a syrinx is an expansion of the central canal (canalicular) or is outside the central canal (extracanalicular) and whether the subarachnoid space is affected by the associated condition may be important factors determining the underlying pathophysiology. Furthermore, there may be different mechanisms for initial cyst formation and subsequent cyst enlargement (Brodbelt and Stoodley 2003).

Essential, but still unresolved aspects of the condition include the composition of syrinx fluid and the pressure within syrinx cavities relative to the subarachnoid space. Each of these will be discussed, following a general outline of the history of theories regarding syringomyelia pathogenesis.

6.2 History of Filling Mechanism Theories

Original descriptions of syringomyelia were garnered from autopsy studies. The pathological appearances were therefore of a collapsed cavity, rather than the tense cyst, exerting pressure on the surrounding cord tissue, that is now familiar to neurosurgeons. Initial theories regarding pathogenesis were accordingly not focused on fluid dynamics. Chiari and Ollivier D'Angers both suggested that syrinx cavities were developmental defects of the central canal or spinal cord (Newton 1969; Ollivier 1827). A subsequent theory was that the cavities were formed secondary to tissue loss, and attention turned to ischaemia as a possible cause (Joffroy and Achard 1887). Early experimental studies continued to focus on tissue loss and vascular effects of arachnoid inflammation and scarring (Hall et al. 1975; McLaurin et al. 1954; Woodard and Freeman 1956). Ischemic tissue loss was considered by Caplan and colleagues to be an important component of syringomyelia associated with arachnoiditis, although the authors suggested that alterations of CSF dynamics could contribute to cavity formation (Caplan et al. 1990).

Traumatic birth then received attention as a possible causative factor. It was suggested that the high pressure applied to the foetal head during a difficult labour and the use of forceps may increase venous pressure, displace the cerebellar tonsils, cause the central canal to rupture, or cause haemorrhage that results in arachnoiditis (Newman et al. 1981; Williams 1977; Hida et al. 1994).

A hydrodynamic aetiology was first proposed by Cleland, who suggested that brainstem abnormalities led to hydrocephalus and dilation of the central canal (Cleland 1883). Gardner refined this theory, proposing that obstruction of the outlets of the fourth ventricle led to both hydrocephalus and an enlarged central canal which, in extreme cases, would rupture and manifest as myelomeningocele (Gardner 1959; Gardner and Angel 1958). Williams proposed an alternative explanation by which fluid could be forced from the fourth ventricle into the central canal, implicating mobile cerebellar tonsils as a variable plug that would lead to pressure differentials between the head and the spine (Williams 1969, 1972).

A hydrodynamic mechanism, forcing CSF from the spinal subarachnoid space across the cord parenchyma, was first proposed by Ball and Dayan, who suggested that increases in CSF pressure caused by coughing and sneezing would force fluid into the cord (Ball and Dayan 1972). Different pathways and dynamics of transmedullary CSF flow have subsequently been proposed by Oldfield and colleagues (Heiss et al. 1999; Oldfield et al. 1994), Stoodley and colleagues (Bilston et al. 2003, 2006, 2010; Brodbelt et al. 2003a, b; Stoodley et al. 1997, 1999, 2000), Carpenter and colleagues (2003), Klekamp and colleagues (2001), and Elliott and colleagues (2009).

Rather than increased flow into syrinx cavities, some authors have argued that the problem is a blockage of fluid outflow. This was first proposed by Aboulker, who postulated that

blockage at the foramen magnum prevented CSF from draining from the central canal into the fourth ventricle (Aboulker 1979). Similarly, Koyanagi and Houkin suggested that fluid accumulates because of an impairment in extracellular fluid absorption (Koyanagi and Houkin 2010), and Klekamp has suggested that blockage of perivascular spaces or cord tethering could affect outflow (Klekamp 2002).

Over the last two decades, some authors have suggested sources of fluid other than CSF. Greitz argued that an increase in intramedullary pulse pressure results in expansion of the cord and that the expanded space fills with extracellular fluid (Greitz 2006). Chang and Nakagawa proposed that syrinx fluid comes from the central canal when there is a lowering of the adjacent subarachnoid pressure (Chang and Nakagawa 2004). Levine has suggested that pressure exerted by a Chiari malformation causes an increase in the spinal cord venous pressure, with vascular damage allowing plasma filtrate to pass across the vessel walls (Levine 2004).

Investigating detailed fluid physiology is often impossible in patients and difficult in experimental animals. Over recent years, computational and physical modelling techniques have been used to investigate numerous theories regarding CSF physiology in the subarachnoid and perivascular spaces (Bertram et al. 2008; Bilston et al. 2003, 2006, 2010; Berkouk et al. 2003; Carpenter et al. 2003; Martin et al. 2005; Loth et al. 2001; Elliott et al. 2009). Refinements of these techniques may prove extremely useful in adding to our understanding of syrinx pathophysiology.

Recent attention has turned to molecular and cellular contributions to syrinx pathophysiology. Disruption of the blood-spinal cord barrier as a source of fluid has been proposed by several investigators (Ravaglia et al. 2007; Hemley et al. 2009; Levine 2004). Alterations in aquaporin expression have recently been proposed to either increase fluid load or impair fluid outflow (Nesic et al. 2006).

With improved diagnostic imaging, a greater understanding of the pathological anatomy of syringomyelia has developed. It is now known that syrinx cavities associated with Chiari malformation are expansions of the central canal, whereas those associated with spinal cord injury usually start outside the central canal (Milhorat et al. 1995a, b). It has been demonstrated that syrinx cavities are usually not in communication with the fourth ventricle. New dynamic imaging techniques may prove extremely helpful in understanding syrinx pathophysiology (Gottschalk et al. 2010).

6.3 Syrinx Fluid Composition and Pressure

Two crucial factors that could be indicators of syrinx fluid origins and physiology are its composition and pressure. For example, a biochemical composition similar to that of CSF would provide evidence for an origin from CSF, although extracellular fluid would also remain a possibility. It is generally assumed that the composition of syrinx fluid is identical to that of CSF and that this implies that the origin of the fluid is CSF from the subarachnoid space. In fact, there is little direct evidence to support this concept, with only a number of case reports comparing the composition of syrinx fluid with CSF. Most studies have examined the protein content, and there are minimal data on other biochemical parameters. In a study of nine post-traumatic syrinx patients, Rossier and colleagues reported a higher syrinx protein content of 0.35–3.9 g/L (mean 1.15) when compared with cisternal CSF protein of 0.1–0.44 g/L (mean 0.24) (Rossier et al. 1985). Other authors have reported syrinx protein levels ranging from 0.28 to 2.24 g/L (mean 0.88) and a cisternal CSF protein ranging from 0.14 to 0.28 g/L (mean 0.18) (Barnett 1973; Laha et al. 1975; Nurick et al. 1970; Werner et al. 1969; Freeman 1959). Similarly, the fluid in tumour cases has been reported to have a higher protein content than CSF (Lohle et al. 1994). In contrast, Shannon and colleagues reported identical levels of protein in syrinx fluid and CSF in 10 of 13 post-traumatic syrinx patients treated with a syringotomy (Shannon et al. 1981). In 17 of 48 patients, Schlesinger and co-workers obtained percutaneous aspirates of spinal fluid from

the central canal and subarachnoid space (Schlesinger et al. 1981). The syrinx protein content was below 0.5 g/L, which was the same or less than the simultaneous sample obtained from the subarachnoid space.

For a syrinx cavity to enlarge, the pressure within it must exceed the subarachnoid space pressure. The degree of enlargement depends on the pressure difference and the stiffness of the spinal cord tissue. Any proposed mechanism for syrinx expansion must therefore provide an explanation for a higher pressure within the cyst than in the subarachnoid space: simply invoking increases in subarachnoid space pressure is not a sufficient explanation. Of course, spinal pressures are pulsatile, and it may be that the pulsations are more important than mean pressures or that the timing of relationships among syrinx, arterial, and CSF pulsations is important. A vital step in investigating these issues would be to perform simultaneous syrinx and subarachnoid space pressure measurements in awake, ambulatory patients. Pressures within syrinx cavities are obviously difficult to measure directly under these conditions. Pressure measurements taken with patients anaesthetized, under positive pressure ventilation and positioned prone, may have no relationship to the pressure in awake, ambulatory patients. Studies using MRI and computational modelling techniques (Battal et al. 2011; Shaffer et al. 2011) may provide some assessment of CSF flow dynamics, but cannot directly measure pressure, and cannot be used to compare syrinx and subarachnoid space pressures.

In a pioneering study of pressures, Ellertsson and Greitz performed percutaneous measurements of syrinx and subarachnoid space pressures in ten patients (Ellertsson and Greitz 1970). They reported a higher pressure in the syrinx in most patients, but the difference was not significant. Perhaps the most detailed study of pressures in awake patients is that of Heiss and colleagues, who studied cervical and lumbar subarachnoid pressures in patients with Chiari malformation and syringomyelia, both while they were awake and during surgery (Heiss et al. 1999). Compared to controls, they found that cervical subarachnoid mean pressure and pulse pressure were increased and that compliance was reduced. After posterior fossa decompression, the spinal subarachnoid pressure and pulse pressure returned to normal. They also measured syrinx pressure and subarachnoid pressure during surgery and found the two pressures to be identical (Heiss et al. 1999). Application of a Valsalva manoeuvre during surgery produced no significant difference between cranial and spinal subarachnoid pressures. This is in contrast to a report by Williams, who found that Valsalva manoeuvres created transient differences between spinal and cranial pressures (Williams 1981).

It is apparent that only sparse information exists regarding the crucial elements of syrinx fluid composition and pressure. In our opinion, it is unlikely that a complete understanding of syrinx pathophysiology will unfold without more detailed studies of these aspects in patients.

6.4 Hydrodynamic Mechanisms

Contemporary theories of syringomyelia pathogenesis have largely focused on alterations of CSF pressure, pulsations, and flow that drive fluid into the spinal cord. These are referred to here as ‘hydrodynamic mechanisms’ and are divided into those that implicate a flow from the fourth ventricle into the central canal and those that involve fluid flowing across the cord parenchyma from the subarachnoid space, mechanisms limiting outflow, and pressure effects on the cord causing dissection of cord tissue by an existing syrinx.

6.4.1 Flow from the Fourth Ventricle

Gardner refined the original hypothesis of Cleland, suggesting that obstruction of the fourth ventricle outlets resulted in expansion of the central canal as part of the same process leading to hydrocephalus (Gardner and Angel 1958). In this model, a ‘water-hammer’ effect is created, with each arterial pulsation causing an increase in intracranial pressure that is transmitted directly into the central canal, expanding it to form a syrinx (Fig. 6.1). Gardner argued that the subarachnoid space normally forms when the

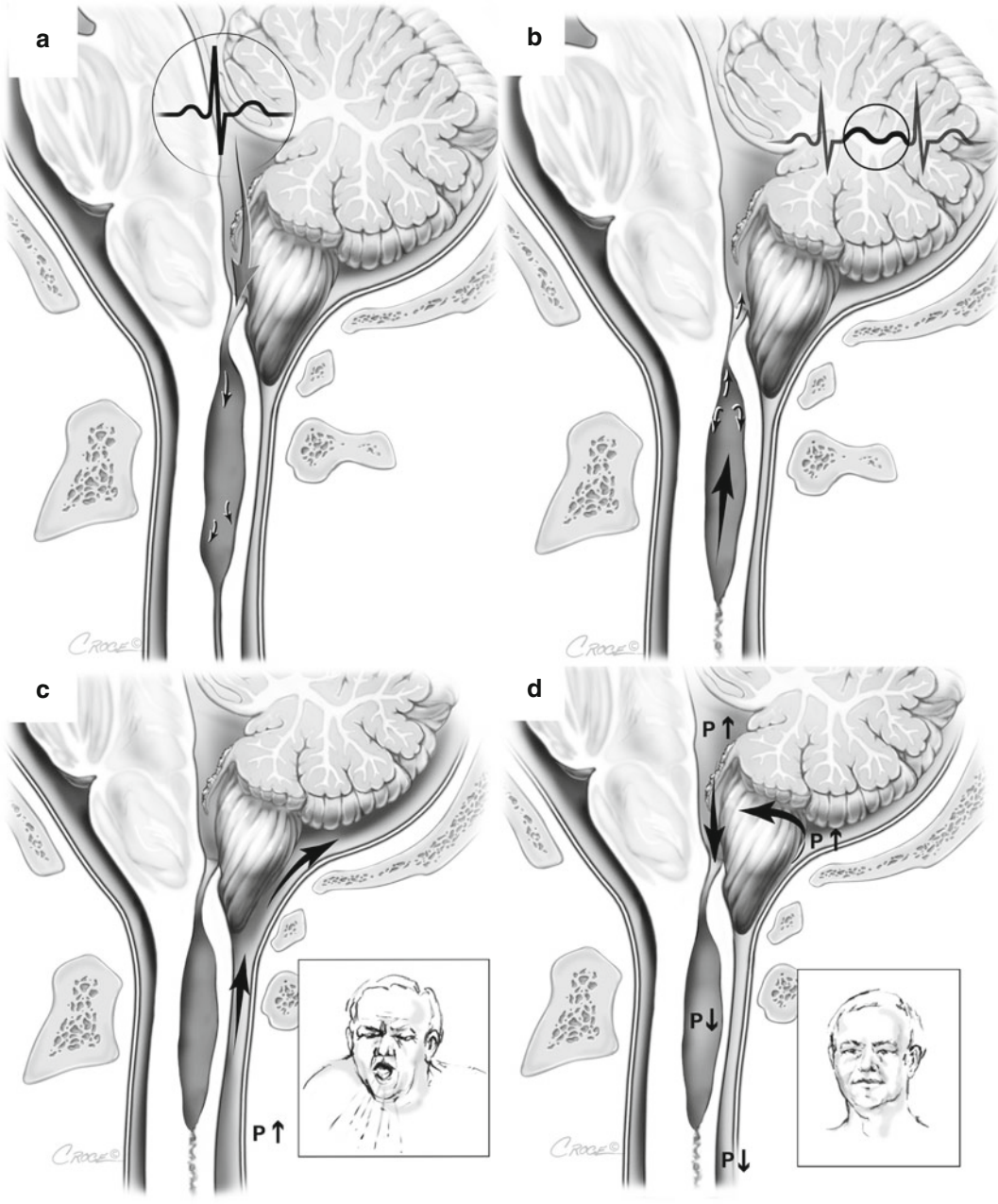

Fig. 6.1 Proposed syrinx filling mechanisms involving fluid flow from the fourth ventricle. Theory proposed by Gardner et al. (1957). (**a**) During systole, CSF is forced into the central canal. (**b**) During diastole the canal is closed and fluid cannot return to the fourth ventricle. Theory proposed by Williams (1970). (**c**) During Valsalva manoeuvres, CSF is forced from the spine into the cisterna magna. (**d**) After relaxing, the cerebellar tonsils act as a valve, preventing fluid returning to the spinal subarachnoid space. Fluid is therefore forced into the fourth ventricle and then into the syrinx. There is now abundant evidence that these theories do not explain the vast majority of syrinxes

CSF pressure in the fourth ventricle ruptures through the foramina of Magendie and Luschka. He considered there to be a spectrum of resulting abnormalities, with hydrocephalus, Chiari malformation, and syringomyelia at the less severe end and open myelomeningocele at the more

severe end (Gardner and Angel 1958). He also suggested that syringomyelia in association with other conditions such as spinal cord injury was coincidental and that such cases also had an underlying Chiari malformation.

Much of Gardner's hypothesis appears to hold for syringomyelia in association with Chiari II malformation. In these cases, there is continuity between the expanded central canal and the fourth ventricle, and there is hydrocephalus (Milhorat et al. 1995a, b). The hydrocephalus and syringomyelia both resolve with ventricular shunting.

For other types of syringomyelia, which form the majority, there has been an accumulation of strong evidence against Gardner's hypothesis: the subarachnoid space forms prior to the opening of the fourth ventricle outlets during development; there is usually no continuity between the fourth ventricle and the syrinx; the outlets of the fourth ventricle are not always obstructed in cases of Chiari I malformation; and Chiari malformation is not the only condition associated with syringomyelia.

Williams developed an alternative explanation for a force driving fluid from the fourth ventricle into the central canal (Williams 1970, 1972). He proposed that the outlets of the fourth ventricle are not obstructed and that fluid enters the cranial subarachnoid space when the spinal subarachnoid pressure increases with coughing and sneezing (Fig. 6.1). The cerebellar tonsils would then act like a valve to prevent fluid flowing back into the spinal subarachnoid space, resulting in a pressure differential between the cranial and spinal cavities. The only available pathway for fluid in the cranial subarachnoid space to reach the spine to restore pressure equilibrium would then be for it to flow into the fourth ventricle and then to the central canal, causing it to expand.

Evidence against this proposed mechanism includes the fact that syrinx cavities are not usually in continuity with the fourth ventricle and that syringomyelia occurs in association with other posterior fossa abnormalities and tumours that would not be expected to have the same valve mechanism as was proposed for the cerebellar tonsils in Chiari malformation.

The evidence against a direct flow of fluid from the fourth ventricle into the central canal or syrinx is compelling. Although posterior fossa decompression remains the mainstay of treatment for syringomyelia associated with Chiari malformation, this does not appear to be due to correction of the abnormalities proposed by Gardner or Williams. Plugging of the opening of the central canal is no longer recommended as part of this procedure (Vanaclocha et al. 1997; Ball and Dayan 1972).

6.4.2 Trans-parenchymal Flow

If the fluid in syrinx cavities is CSF and it has not reached the cavity directly from the fourth ventricle, it must flow across the cord tissue from the subarachnoid space. There has been much speculation about the possible route of such a fluid flow and the forces driving it.

In contrast to the proposal by Williams, Ball and Dayan suggested that a Chiari malformation would act to prevent spinal CSF from entering the cranial compartment during Valsalva manoeuvres (Fig. 6.2). They then speculated that the resulting increase in spinal CSF pressure could force CSF into perivascular spaces in the cord and that this fluid could coalesce to form a syrinx (Ball and Dayan 1972). Subarachnoid space obstruction from other causes such as post-traumatic arachnoiditis was said to produce a similar mechanism for fluid entry into the cord (Ball and Dayan 1972). The authors pointed to the pathological finding of enlarged perivascular spaces in syrinx cases as evidence for this theory.

Oldfield and colleagues proposed a similar mechanism, whereby the Chiari malformation imparts a piston-like effect on the spinal subarachnoid space, forcing fluid through either the perivascular spaces or interstitial spaces (Fig. 6.2) (Oldfield et al. 1994; Heiss et al. 1999). These authors provided cine-MRI and intra-operative ultrasound evidence of cerebellar tonsil movement in support of their theory, but had no direct evidence for fluid flow into the cord.

Support for a perivascular flow of fluid has arisen from the experimental work of Stoodley

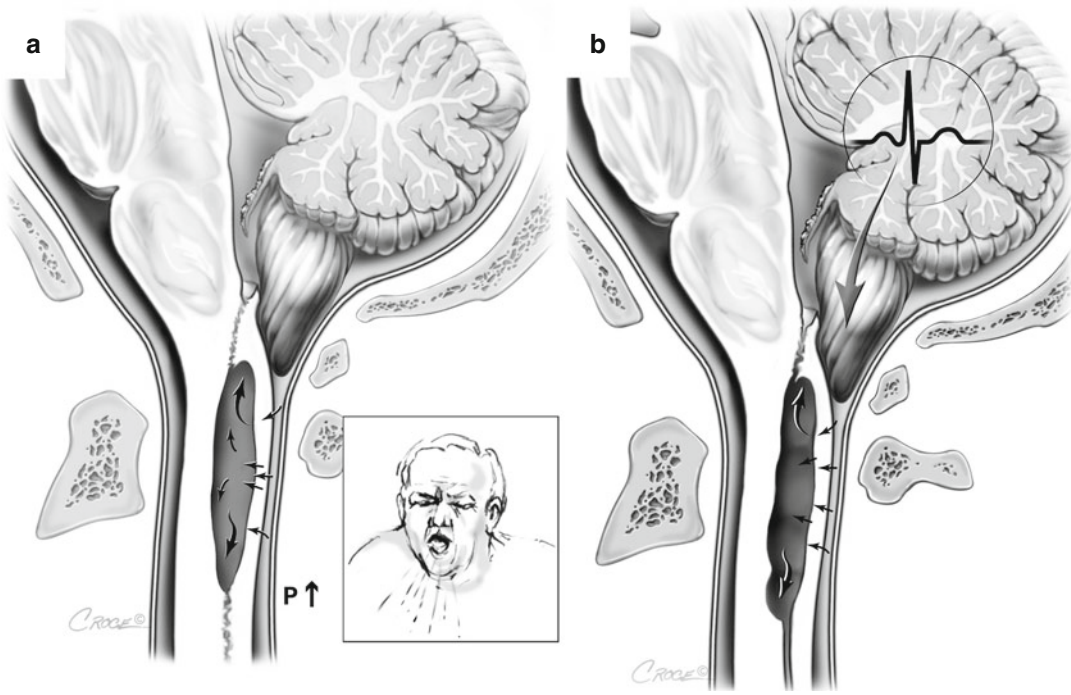

Fig. 6.2 Proposed trans-medullary filling mechanisms. Theory proposed by Ball and Dayan (1972). (**a**) The Chiari malformation acts to isolate the spinal subarachnoid space and that Valsalva manoeuvres increase the subarachnoid space pressure, forcing fluid into the cord. Theory proposed by Oldfield et al. (1994). (**b**) The cerebellar tonsils act as a 'piston' with each systole to increase spinal subarachnoid pressure and force fluid into the cord. These theories cannot explain expansion of a syrinx cavity, because the pressure in the cavity must exceed subarachnoid pressure for it to do so

and colleagues, who used tracers of CSF bulk flow to demonstrate perivascular flow from the subarachnoid space to the central canal in normal animals (Stoodley et al. 1996, 1997), and from Klekamp et al., who showed oedema and enlarged perivascular spaces in a model of arachnoiditis (Klekamp et al. 2001). Further work showed that perivascular flow of CSF from the subarachnoid space occurs in models of canalicular and extracanalicular syringomyelia (Fig. 6.3) (Stoodley et al. 1999; Brodbelt et al. 2003b) and that flow is dependent on arterial pulsations (Stoodley et al. 1997).

A major problem with any proposed explanation for syrinx formation from a transparenchymal flow of CSF from the subarachnoid space is the simple physical fact that increasing pressure on the outside of the cord cannot create an expanding cyst within the cord. For a cavity to enlarge, the pressure within it must exceed the surrounding pressure, and this cannot occur with flow that is driven by an increase in pressure in the subarachnoid space. Several investigators have attempted to address this. Bilston and colleagues have examined the pulsatile properties of fluid flow in perivascular spaces and the subarachnoid space (Bilston et al. 2003, 2010). Using computational modelling, they demonstrated that the anatomical characteristics of the perivascular space could act as a 'leaky' one-way valve for pulsatile CSF flow. In addition, a timing mismatch between the arterial wave and CSF pressure wave arriving at the interface between the subarachnoid space and the perivascular space could act to increase flow (Fig. 6.4). They indicate this occurs when the CSF peak pressure occurs at a different time to the arterial pulse peak pressure, resulting in lower resistance to CSF inflow than outflow (Bilston et al. 2010). It was suggested that Chiari malformation and other obstructions in the subarachnoid space could act to create the timing mismatch.

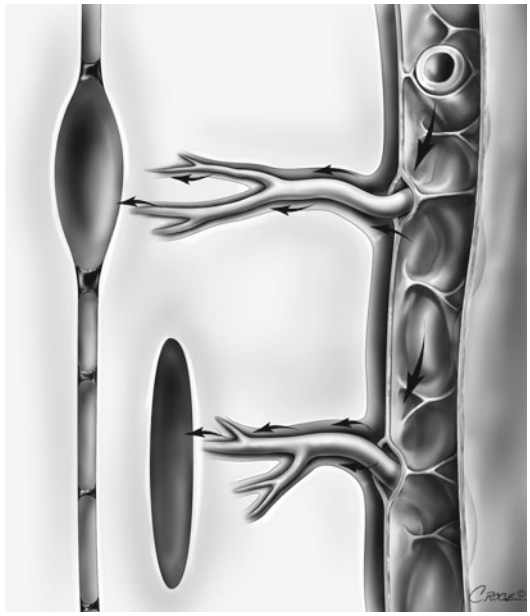

Fig. 6.3 Perivascular spaces as a proposed pathway for CSF flow in both canalicular and extracanalicular syringomyelia. Flow from the subarachnoid space enters the perivascular spaces, which narrow as they penetrate deeper into the cord. Possible mechanisms for such a flow to create a higher mean syrinx pressure than mean subarachnoid pressure include a partial valve effect of the perivascular space and a mismatch in the timing of the arterial and CSF pulse waves (Bilston et al. 2003, 2010)

An alternative explanation is that stenosis of the subarachnoid space could lead to a focal increase in pressure in the spinal cord with Valsalva manoeuvres, the so-called 'elastic jump' (Carpenter et al. 2003). Although computational modelling has shown this to be a theoretical possibility, the magnitude of the effect appears to be too small to be significant (Elliott et al. 2009).

6.4.3 Obstruction of Outflow

It appears likely that there is a continual flow of fluid into the spinal cord and also into syrinx cavities. Unless a syrinx is enlarging, the outflow must equal the inflow. The physiology of fluid outflow is not known, but one possible explanation for syrinx formation and enlargement is the obstruction of outflow. This concept was initiated by Ellertsson and Greitz, who measured syrinx and subarachnoid space pressures in patients, showing higher pressure in syrinx cavities, although this was not significant. They suggested an impairment of outflow, although did not speculate as to the mechanism of this (Ellertsson and Greitz 1970).

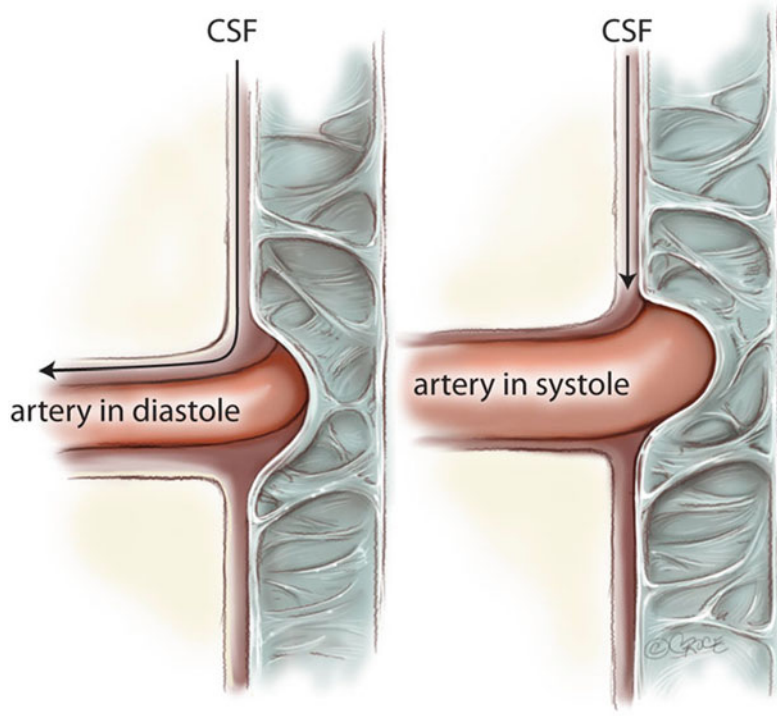

Fig. 6.4 A phase difference in pulsations may explain a valvelike effect of perivascular flow. Obstructions of the subarachnoid space could be responsible for slowing the pulse transmission to create a phase mismatch. If the CSF systolic wave arrives at the cord surface during arterial diastole, the perivascular space will be open, and flow will be greater than if the CSF pulse arrives during arterial systole, when the perivascular space will be smaller (Bilston et al. 2010)

Aboulker suggested that the pressure on the spinal cord at the cervicomedullary junction prevents CSF draining rostrally along the central canal to the fourth ventricle (Aboulker 1979). Although such a rostral flow has been demonstrated in experimental animals, it is not known whether this occurs in humans (Milhorat et al. 1991). Theoretically, fluid could also drain through spinal cord parenchyma, and cord compression might compress the extracellular space or reduce permeability, thus restricting outflow.

Recently, Koyanagi and Houkin have suggested that an increase in spinal venous pressure might impair absorption of extracellular fluid, resulting in accumulation of fluid in the cord and syrinx formation (Koyanagi and Houkin 2010).

There is little clinical or experimental evidence to support or refute these theories. The physiology of fluid outflow from the spinal cord and syrinx cavities is a largely unexplored area that may be important in syringomyelia physiology and is deserving of more research attention.

6.4.4 Transmitted Pressure Effects on Existing Cavities

Rather than fluid being forced into the cord by pressure changes in the subarachnoid space or physiological changes in perivascular flow, an alternative view is that pressure exerted on the cord surface causes rostral-caudal dissection of an existing cavity, leading to enlargement of the cavity. This concept began with the description by Williams of a 'suck and slosh' mechanism for expansion of post-traumatic syrinx cavities. He suggested that increases in pressure in the subarachnoid space cause pressure on a cavity, which then dissects into the surrounding cord tissue, enlarging the potential space for the cavity, which then fills with extracellular fluid (Williams 1992). This mechanism has also been supported by the work of Oldfield and colleagues (Oldfield et al. 1994), who used intra-operative ultrasound to show that the cord and syrinx became compressed with each arterial pulsation and in synchrony with the descent of the cerebellar tonsils of a Chiari malformation. They suggested that this compression would cause extension of the syrinx cavity and that the fluid filling the cavity came from the subarachnoid space.

These theories rely on the presence of an initial cavity that can subsequently be enlarged by the putative dissection process. It is possible that this may apply to post-traumatic syringomyelia, where initial cavities form from haemorrhage and ischaemia. However, there is no evidence for a similar process in those cases associated with Chiari malformation. In addition, this process could at best explain the enlargement of a syrinx but not an increase in pressure relative to the subarachnoid space.

6.4.5 Summary of Hydrodynamic Theories

The available evidence does not support a fourth ventricular origin for syrinx fluid. There is good evidence that at least some syrinx fluid originates from the subarachnoid space and that the route of this fluid flow is via the perivascular spaces. However, theories that invoke increases in subarachnoid space pressure as the driving force are not sufficient to explain syrinx formation and enlargement. It is possible that complex relationships between CSF and arterial pulsations or the anatomical characteristics of the perivascular spaces explain the accumulation of fluid inside the cord. Pulsations exerted on the surface of the cord may contribute to cord tissue damage but seem insufficient to explain the development of high-pressure cavities. The possible role of perturbations in fluid outflow remains largely unexplored.

6.5 Other Sources of Fluid

None of the hydrodynamic theories have adequately explained syrinx formation and enlargement. Alternative theories have been put forward to suggest that syrinx fluid is not of CSF origin and that hydrodynamic factors driving CSF flow are not responsible. These proposed mechanisms have been used to explain the development of cavities in association with intramedullary tumours, or have suggested that syrinx fluid is derived from interstitial fluid, or

originates through abnormalities of the blood-spinal cord barrier or even cellular fluid transport mechanisms.

6.5.1 Tumours

Syringomyelia occurs in association with posterior fossa tumours and with spinal extramedullary and intramedullary tumours. In general, it is reasonable to propose that the filling mechanism in posterior fossa tumour cases may be similar to the process that occurs with Chiari malformation and may be hydrodynamic in origin. Spinal extramedullary tumours may act by causing partial blockage of the subarachnoid space and could be thought of as having a similar underlying aetiology to cases associated with spinal arachnoiditis.

The particular tumour type that is likely to have a unique pathophysiology is the intramedullary tumour. Although expansion of the cord could theoretically result in obstruction of the subarachnoid space, it is our experience that many tumours are small and the subarachnoid space does not appear to be affected in the majority of cases. Intramedullary tumours with particularly high rates of syrinx development include haemangioblastomas and ependymomas (Samii and Klekamp 1994).

A possible explanation for syrinx development in association with intramedullary tumours is that the cystic cavity is part of the tumour itself (Barnett 1973), but for some tumour types at least, the syrinx wall is gliotic tissue (Lohle et al. 1994). There is limited information regarding the composition of tumour-associated syrinx fluid, but there is some evidence that it is high in protein (Lohle et al. 1994), suggesting that the fluid comes directly from the tumour or its vasculature.

It has been suggested that, in haemangioblastomas, the vasculature is leaky and the interstitial pressure is high, leading to extravasation of plasma (Lonser et al. 2006). In support of this hypothesis, Lonser et al. have reported a case demonstrating progressive leakage of contrast medium from a haemangioblastoma into the surrounding cord tissue (Lonser et al. 2006).

Samii and Klekamp argue that the pathophysiology is likely to include some abnormality of CSF flow in addition to secretion of fluid and protein by the tumour. They cite the predominant rostral location of syrinx cavities relative to the tumour and the higher rates of syrinx formation in tumours in the cervical cord to support this view (Samii and Klekamp 1994).

We are not aware of any experimental models of tumour-associated syringomyelia, and the clinical evidence is limited. However, it does seem likely that specific tumour-related factors are more important than CSF dynamics in this type of syrinx.

6.5.2 Interstitial Fluid

Interstitial fluid has been proposed by numerous authors as a source of syrinx fluid. One line of reasoning is that tethering of the cord by arachnoiditis results in tensile radial stress, which lowers the pressure in the cord and leads to inflow of extracellular fluid (Bertram et al. 2008).

Josephson and colleagues provided experimental evidence for a theory that pulse transmission through the cord, past a region of subarachnoid block, would cause expansion of the cord below the block (Josephson et al. 2001). The proposal is that, with each arterial pulsation, the pulse wave in the subarachnoid space is blocked, but the wave in the cord continues, creating a higher pressure in the cord than in the surrounding subarachnoid space, thus expanding the cord. The expanded cord would then fill with extracellular fluid. A similar explanation was proposed and tested using an electrical circuit model of CSF dynamics (Chang and Nakagawa 2003, 2004). In this model, the pressure was transmitted down the central canal, forcing fluid out of this channel, below the level of the subarachnoid block where the surrounding subarachnoid pressure was lower.

Greitz subsequently proposed a somewhat different explanation (Greitz 2006). He suggested that narrowing of the subarachnoid space causes an increase in CSF velocity at the region of narrowing. The increased fluid velocity has a

Venturi effect, lowering the pressure in the subarachnoid space and causing a suction effect on the cord, expanding it during each systole. According to Greitz, extracellular fluid would accumulate in the expanded cord, forming a syrinx (Greitz 2006).

Klekamp suggested that interstitial fluid could be important in canalicular and extracanalicular cavities, by exceeding the normal fluid capacity of the extracellular space. This might occur due to blockage of perivascular spaces, cord tethering, changes in vascular flow, or obstruction of CSF flow (Klekamp et al. 2002).

In common with the hydrodynamic theories, many of the theories proposing an interstitial fluid origin cannot explain a higher pressure in the syrinx than the spinal cord tissue and subarachnoid space. Instead, they imply passive filling of syrinx cavities, which does not fit with our clinical observation that the pressure in many syrinx cavities appears much higher than the surrounding subarachnoid space.

6.5.3 Blood-Spinal Cord Barrier Disruption

Several authors have suggested that fluid crossing a deficient blood-spinal cord barrier may contribute to syrinx fluid (Fig. 6.5). Clinical case reports have supported a role for barrier disruption, by demonstrating contrast enhancement around syrinx cavities on MR scans (Lonser et al. 2006; Ravaglia et al. 2007).

Levine suggested that the changes in pressure above and below a subarachnoid blockage would be transmitted into the veins, with collapse of vessels rostral to a block and dilation of vessels caudal to the block, causing cord parenchymal stress. This stress would lead to tissue destruction and resultant damage to capillaries, and venules would allow plasma filtrate to pass into the cord (Levine 2004).

A particular case could be made for a role of the blood-spinal cord barrier in post-traumatic syringomyelia. It has been demonstrated that the

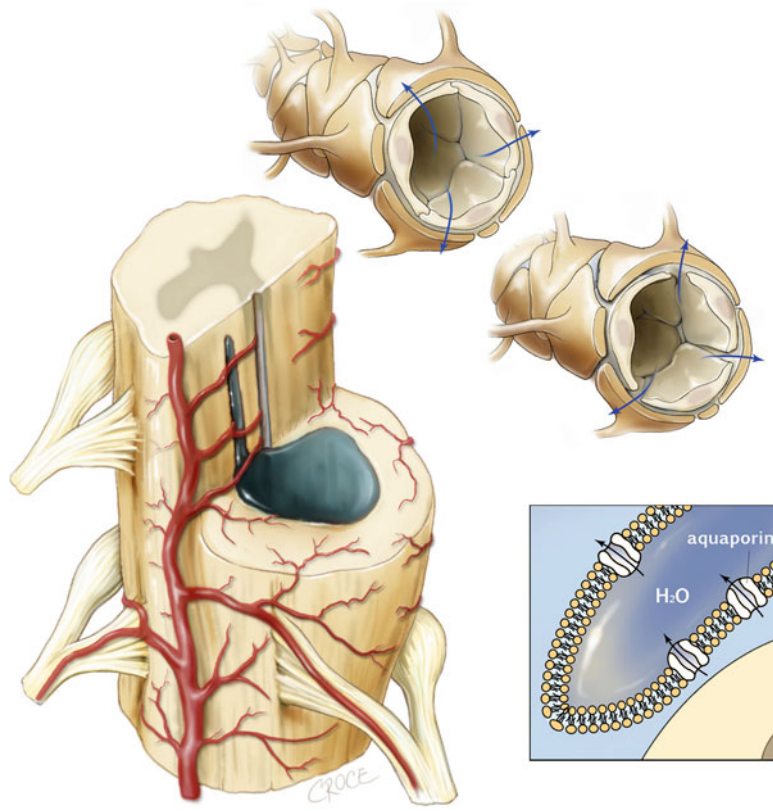

Fig. 6.5 Vascular and tissue sources of fluid or impaired absorption may result in a syrinx pressure higher than the subarachnoid space. *Left*: the syrinx cavity is often in the highly vascular grey matter and surrounded by vessels. *Top* and *top-right*: an impaired blood-spinal cord barrier allows fluid to cross the vessel wall and add to the syrinx volume. *Bottom right*: abnormalities of aquaporin expression may also allow fluid to leak across vessels or may impair absorption of syrinx fluid into the vasculature

barrier is disrupted following spinal cord injury (Mautes et al. 2000), which contributes to spinal cord oedema. In most spinal cord injuries, it is assumed that the barrier is subsequently reconstituted and the oedema subsides. It is possible that a prolonged disruption of the barrier could allow continued fluid leakage and enlargement of an initial haemorrhagic or necrotic cavity. Experimental evidence in a rat model of post-traumatic syringomyelia supports this hypothesis (Hemley et al. 2009).

6.5.4 Aquaporins

The recent discovery of a role of aquaporins in fluid transport in the central nervous system may have implications for syringomyelia pathogenesis. Aquaporin-4 is the most abundant type in the brain and spinal cord and is expressed on astrocyte and ependymal membranes around the blood-brain barrier and brain-CSF interfaces. Studies of aquaporin-4 in spinal cord injury have reported conflicting results, with some authors finding an early downregulation and later upregulation (Nesic et al. 2006) and other investigators finding an early upregulation (Saadoun et al. 2008). It is possible that changes in aquaporin expression could either enhance the movement of water into the central canal or alternatively prevent water from moving from the central canal into the parenchyma. These mechanisms may contribute to the enlargement of the central canal in Chiari-associated syringomyelia. A case of syringomyelia in a patient with anti-aquaporin antibodies has recently been reported, with the authors suggesting that a reduction in aquaporin expression may have resulted in permeability of the blood-spinal cord barrier (Sakabe et al. 2010).

There are very few experimental studies of aquaporins in syringomyelia. Sun and colleagues found a downregulation of aquaporin-4 in the early stages of syrinx formation in a rabbit canalicular model and suggested that this played a role in oedema formation (Sun et al. 2007). Our own work has demonstrated an increase in aquaporin expression around cavities in post-traumatic syringomyelia (Hemley et al. 2013) but not around cavities in canalicular syringomyelia (Hemley et al. 2012). Regardless of whether aquaporin disturbances play a role in syrinx initiation, our view is that they are likely to have an important function in fluid transport in or out of syrinx cavities.

6.6 Outstanding Questions

At the beginning of this chapter, we suggested that close inspection of the pathophysiology underlying syringomyelia reveals complexity. Unfortunately, rather than elucidating the syrinx filling mechanism, the plethora of theories described above has added to this complexity. Many of the theories provide divergent opinions on basic concepts such as whether syrinx fluid is CSF, interstitial fluid, or plasma; whether the cerebellar tonsils in Chiari malformation allow fluid to pass from the head to the spine or vice versa; whether the subarachnoid space pressure is elevated or reduced; and whether syrinx cavities expand by fluid being forced in or by sucking fluid in. We do not think that major advances will be made in the understanding of syrinx filling mechanisms until the following fundamental questions are answered by careful clinical and experimental studies:

- What is the chemical composition of syrinx fluid in the various types? Is the fluid CSF, interstitial fluid, plasma, or a mixture of these?
- What is the relationship between syrinx pressure and subarachnoid space pressure?
- What is the relationship between syrinx and subarachnoid space pulse pressures?

In addition to these fundamental questions, much greater detail is required regarding fluid inflow and outflow pathways, the role of the blood-spinal cord barrier and aquaporins, and the precise mechanism at play with each associated condition.

Conclusions

Despite the myriad theories proposed regarding syrinx pathogenesis, an objective appraisal would suggest that very little is certain regarding even the fundamental

principles. The goal of a single unifying theory remains unlikely to be fulfilled until these are elucidated. It remains likely that different syrinx subtypes have different filling mechanisms and much work remains to be done to clarify these.

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