# Mechanisms of action of fascial plane blocks: a narrative review

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### ABSTRACT

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Received 16 November 2020 Revised 30 December 2020 Accepted 4 January 2021 **Background** Fascial plane blocks (FPBs) target the space between two fasciae, rather than discrete peripheral nerves. Despite their popularity, their mechanisms of action remain controversial, particularly for erector spinae plane and quadratus lumborum blocks. **Objectives** This narrative review describes the scientific evidence underpinning proposed mechanisms of action, highlights existing knowledge gaps, and discusses implications for clinical practice and research.

Findings There are currently two plausible mechanisms of analgesia. The first is a local effect on nociceptors and neurons within the plane itself or within adjacent muscle and tissue compartments. Dispersion of local anesthetic occurs through bulk flow and diffusion, and the resulting conduction block is dictated by the mass of local anesthetic reaching these targets. The extent of spread, analgesia, and cutaneous sensory loss is variable and imperfectly correlated. Explanations include anatomical variation, factors governing fluid dispersion, and local anesthetic pharmacodynamics. The second is vascular absorption of local anesthetic and a systemic analgesic effect at distant sites. Direct evidence is presently lacking but preliminary data indicate that FPBs can produce transient elevations in plasma concentrations similar to intravenous lidocaine infusion. The relative contributions of these local and systemic effects remain uncertain.

**Conclusion** Our current understanding of FPB mechanisms supports their demonstrated analgesic efficacy, but also highlights the unpredictability and variability that result from myriad factors at play. Potential strategies to improve efficacy include accurate deposition close to targets of interest, injections of sufficient volume to encourage physical spread by bulk flow, and manipulation of concentration to promote diffusion.

### INTRODUCTION

Regional anesthesia is generally thought of as placing a needle into close proximity to a discrete nerve or plexus (originally guided by mechanical elicitation of paresthesia, then by neurostimulation, and now most commonly by ultrasound imaging) followed by injection of local anesthetic around these nerves. Fascial plane blocks (FPBs) are a relatively new class of regional anesthesia techniques, distinguished by the fact that the target of needle insertion and local anesthetic injection is a compartment (the 'plane') between two anatomically separate layers of fascia and there is no attempt to locate individual nerves. Blockade of afferent nociceptive transmission nevertheless remains the ultimate goal.

This is not a new concept—long-established techniques such as the landmark-guided ilioinguinaliliohypogastric and fascia iliaca blocks are essentially FPBs. Nevertheless, the ability to easily visualize and target fascial planes with ultrasound imaging has led to an explosion in the number of described FPBs, especially of the torso. Their popularity stems from their ease of performance, perceived safety (especially with regard to needle-nerve trauma), and ability to provide meaningful analgesia in a variety of clinical settings.<sup>1-11</sup> However, there is controversy over how they produce their clinical effect,<sup>12-14</sup> mainly because they do not behave like traditional regional anesthesia techniques. In particular, (1) dense neural blockade is rarely seen; (2) there is variability in the results obtained in individual patients; (3) and the patterns of cutaneous sensory blockade often under-represent the analgesia that is observed. The objectives of this article are to review the scientific principles and evidence that underpin the proposed mechanisms of action underlying the effect of FPBs, to identify the knowledge gaps that exist, and to discuss the implications for clinical practice and research.

### Dispersion of local anesthetic following injection into a fascial plane

The movement of fluid molecules occurs via two distinct processes. The first is bulk flow (also known as mass flow), where fluid moves as a 'body' of aggregated particles, driven by a pressure gradient. Bulk flow of fluid in human tissues is constrained by fascia, which at a macroscopic level are densely interwoven barriers of collagen fibers.<sup>15</sup> The space, or plane, between layers is filled with adipose cells, collagen and elastic fibers of loose connective tissue, and a hydrated glycosaminoglycan matrix (ground substance). This plane is readily distended by the hydraulic pressure of fluid injection-the hydrodissection phenomenon familiar to practitioners of ultrasound-guided regional anesthesia (figure 1). The pattern and limits of bulk flow within the plane are governed by physical forces that include the velocity and direction of injection, elastic recoil of the distended fascial plane, and the sliding movement of the fascial layers that occurs with subsequent muscular contraction and movement. This last factor may explain the continued increase in distribution area over several hours, as has been observed with serial MRI scans following transversus abdominis plane (TAP) blocks in human volunteers (figure 2).<sup>16</sup>

The second process is *diffusion*, in which there is net movement of particles within a fluid medium

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**Figure 1** (A) Ultrasound image of the anterolateral chest over pectoralis major (PM) and pectoralis minor (Pm). The fascial layer demarcating the plane between pectoralis minor and serratus anterior (SA) muscle is shown by the white arrows. Note the multilamellar appearance of the layer. (B) Bulk flow of local anesthetic injection (illustrated by the block arrows) into the fascial plane has separated SA and Pm muscles. Local anesthetic will also gradually diffuse across the perimysium of the muscles (illustrated by the dotted arrows).

driven by a concentration gradient. Fascia is not a barrier to diffusion, as at the *microscopic* level, the pores between the interlinked collagen fibers render fascia freely permeable to local anesthetic drug molecules. Local anesthetic can therefore cross fascial layers even in the absence of macroscopic perforations.

There are thus three possible fates for local anesthetic molecules injected into a fascial plane: (1) they spread out and remain within the interstitial compartment of the plane; (2) they disperse out of the plane into adjacent muscles or tissue compartments via diffusion or bulk flow through macroscopic openings; or (3) they diffuse into blood vessels and are transported within the vascular system to distant tissue sites. Consequently, the potential mechanisms of analgesic action of FPBs can be broadly divided into a local effect on nerves in the vicinity of injection, and a systemic effect resulting from vascular dispersion. The scientific basis, evidence, and areas of uncertainty surrounding these mechanisms are discussed in more detail.

# Local analgesic effect mediated by spread within the interstitial compartment of the plane

The principal aim of FPBs is blockade of impulse generation and propagation in peripheral nerves. Almost all FPBs target clinically



**Figure 2** Progression with time in the visible areas of injectate spread in the transversus abdominis plane (TAP), measured on serial MRI scans, of lateral and subcostal (called 'upper' here) TAP blocks as reported by Børglum *et al.*<sup>16</sup> Dotted line=subcostal TAP block with 15 mL. Dashed line=lateral TAP block with 15 mL. (adapted from Børglum *et al.*<sup>16</sup> with permission)



Figure 3 Cadaver specimen with the subcutaneous tissue removed. Lateral cutaneous branches (LCB) (white numbers) of the intercostal nerves emerge between the digitations of the serratus anterior (SA) muscle. Note the complex branching pattern and anastomoses between adjacent nerves that result in multisegmental sensory innervation of superficial tissues. The second and third LCB in this specimen anastomose to form the intercostobrachial nerve (ICBN). Other nerves in the axilla include branches of the brachial plexus: the medial brachial cutaneous nerve (MBCN), the long thoracic nerve (LTN) and the thoracodorsal nerve (TDN). All of these nerves will potentially be blocked by local anesthetic spread following injection into the fascial plane superficial to the serratus anterior muscle (red X indicates a commonly used location for performance of a superficial serratus plane block). LD, latissimus dorsi muscle; PM, pectoralis major muscle; SCN, supraclavicular nerves. (adapted from Woodworth *et al*<sup>17</sup> with permission)

relevant nerves traveling within the fascial plane of injection. Examples include lateral cutaneous branches of the intercostal nerves innervating the axilla in the PECS2 and superficial serratus anterior plane block (figure 3),<sup>17</sup> as well as branches of thoracoabdominal nerves innervating the muscles and skin of the anterior abdominal wall in the TAP and rectus sheath block.<sup>18</sup> Local anesthetic reaches these nerves by the process of bulk flow and, as with any other peripheral nerve block technique, proceeds to diffuse through the layers of epineurium, perineurium, and endoneurium to block membrane ion channels and prevent the depolarization required for axonal action potential propagation.

This mechanism of action is largely undisputed, except for the observation that discernible cutaneous sensory block following FPBs may be either absent or incongruous with their recommended clinical applications and evidence for benefit. For example, a detailed volunteer study of the lateral TAP block found that cutaneous sensory loss was highly variable in area, and spared large areas of the anterior abdomen in the majority of subjects.<sup>19</sup> This variability has been demonstrated for other FPBs as well.<sup>20–23</sup> Despite this unpredictability in cutaneous sensory blockade, FPBs remain clinically efficacious, as demonstrated by several meta-analyses.<sup>1 2 4–6 11</sup> This has raised questions as to whether peripheral nerve blockade represents the principal mechanism of FPB analgesia in all settings. There are, however, several important considerations that serve to reconcile apparent contradictions in the extent of discernible *cutaneous* sensory blockade and clinically meaningful *analgesia*.

# Anatomical, technical, pharmacokinetic, and physiological factors contributing to variability

The first is that anatomical cutaneous innervation is more complicated than is commonly portrayed in textbooks, particularly over the torso. Nerves branch and anastomose with each other in a complex manner,<sup>24 25</sup> and thus multi-segmental innervation of any patch of skin is the rule rather than the exception.<sup>26</sup> There is also contralateral overlapping innervation across the midline of the anterior torso, which speaks to the importance of bilateral blocks.<sup>27</sup> This, together with expected interindividual anatomical variation, contributes to the patchy and unpredictable pattern of cutaneous loss observed in individuals receiving otherwise identical regional anesthetic blocks.<sup>19–22 28</sup>

Pharmacokinetic variability is another underappreciated consideration to be taken into account. In a unique study of eight human volunteers, Latzke *et al* used microdialysis to measure interstitial fluid concentrations of local anesthetic following a lateral TAP block with 20 mL 0.75% ropivacaine.<sup>29</sup> Sampling was performed from probes placed 2 cm cranial and caudal to the TAP injection site, as well as at a distant site in the contralateral thigh. The intersubject variation in ropivacaine concentrations in the vicinity of the TAP was extremely high, with a 10 000-fold difference between the lowest and highest values recorded in subjects. Sensory block was not assessed in this study, although it is logical to assume that this would have varied in a corresponding manner. An inverse correlation between overall TAP and plasma ropivacaine concentrations led the authors to

postulate that greater redistribution from the TAP occurs in some individuals, although the reasons why this might be so are unclear. These results are highly intriguing but further investigation is required, especially as the individual data from the study do not show a clear association between high TAP and low plasma concentrations or vice versa (figure 4). It is possible that technical error, for example, inconsistency in the precise placement of the microdialysis probes or TAP injection, may have contributed to the wide data dispersion.

More importantly though, as noted in a recent editorial,<sup>30</sup> it would be unrealistic to expect truncal FPBs to achieve the same intensity and consistency of sensory neural blockade as ultrasound-guided peripheral nerve blocks of the limbs, in which generous doses of local anesthetic are precisely deposited around nerves of interest. Simple physics dictates that the further away local anesthetic is injected, the less of it will reach the target. This is compounded by the inherent variability in physical spread of injectate within the fascial plane, as evidenced by a 2.5 to 6-fold difference between subjects in the MRI-visible area of injectate distribution following TAP blocks.<sup>16</sup> A myriad of both technical performance (eg, exact site of injection, accuracy of deposition in plane vs intramuscular, direction of injection. volume injected, speed of injection) and physiological factors (eg, age-related tissue laxity, muscular and fascial contraction and movement, positioning, normal variation in musculoskeletal anatomy and the course taken by nerves) are likely to influence the pattern of bulk flow, and thus the mass of local anesthetic that reaches the target nerves. It is thus difficult to replicate the



**Figure 4** Graphs of ropivacaine concentrations over time adapted from the data of Latzke *et al.*<sup>29</sup> These were measured in the interstitial milieu of the transversus abdominis plane (TAP) at two locations using a microdialysis technique, following a unilateral TAP block with 20 mL 0.75% ropivacaine (150 mg). Ropivacaine concentrations were also measured in plasma, and in the muscle tissue of the contralateral thigh as a representation of distant tissue concentrations. Each colored line represents data from an individual volunteer subject (there are missing data for some measurements and subjects). Note the significant interindividual variability in TAP concentrations, which is much more marked compared with plasma concentration. Differences in redistribution of local anesthetic as an explanation for the variation in TAP concentration have been postulated, though this is not clearly evident from this small study of eight volunteers.

same pattern of sensory block even when an FPB is performed by the same practitioner in the same subject, as shown by significant intraindividual variation in yet another volunteer study of the lateral TAP block.<sup>28</sup>

#### Non-cutaneous contributions to nociception

It is equally important to recognize that cutaneous sensory block is an imperfect surrogate for analgesia, as pain often arises from injury and inflammation of deeper musculoskeletal tissues. Sensory innervation of these different tissues is not always anatomically congruent, as evidenced by the distinction between dermatomes, myotomes, and sclerotomes.<sup>31</sup> They also display different pain characteristics and treatment responses, which are attributed to significant neurobiological differences in the nociceptive pathways.<sup>32-38</sup> Muscles, ligaments, joint capsules, and bone are rich in sensory nerve endings which transduce physical stimuli but normally do not signal pain if these are within physiological limits.<sup>33 35</sup> These 'silent nociceptors' are upregulated by the inflammatory response to tissue injury, with resulting hyperalgesia that manifests as local tenderness and pain on movement.<sup>33 35</sup> Local anesthetic injected into fascial planes close to the site of injury, and which subsequently diffuses through into the surrounding soft tissues, may conceivably inhibit firing of these nociceptors and produce analgesia similar to that achieved by surgical wound infiltration.<sup>39</sup> The importance of introducing local anesthetic into the deeper tissue layers is highlighted by the superior analgesia provided by preperitoneal versus subcutaneous wound infiltration catheters in abdominal surgery, an effect which may even be comparable to that of epidural analgesia.<sup>40</sup> An anti-inflammatory action of local anesthetic, mediated by inhibition of leucocyte chemotaxis and priming,<sup>41–43</sup> may further attenuate the local hyperalgesic response.

Controversy also stems from the fact that some FPBs, such as the PECS1<sup>13</sup> and TAP block,<sup>19</sup> appear to block primarily motor nerves. However, at least a third of fibers within a motor nerve are sensory and nociceptive, and transmit impulses from the afferents located within the tissues that it supplies.<sup>32</sup> Muscle spasm is also a significant source of pain following certain surgeries (eg, breast reconstruction<sup>44 45</sup>); this is attributed to local ischemia secondary to vessel compression in the contracted muscles, with subsequent release of mediators that upregulate silent nociceptors.<sup>46</sup> An important corollary, therefore, is that even if the putative target of FPBs is primarily motor nerves, the ensuing motor block may still contribute to analgesia by relieving muscle contraction and preventing the ischemic inflammatory response.<sup>47 48</sup>

### Differential sensory block

Another reason why cutaneous sensory loss may not always be a definitive measure of neural blockade is that analgesia (meaningful reduction of pain) can be achieved independently of complete anesthesia (absence of all sensation). This is known as *differential block*, a phenomenon consistently observed during the onset and regression of spinal anesthesia and manifesting as earlier onset and larger extent of loss of pinprick and temperature sensation versus light touch.<sup>49–51</sup> Deliberate differential block can also be achieved in clinical practice if appropriately low concentrations of local anesthetic are applied to nerves.<sup>52</sup> The principle is routinely used in modern epidural analgesia<sup>53</sup> and continuous peripheral nerve blocks,<sup>54</sup> and may also apply to truncal FPBs where the injected mass of local anesthetic is widely dispersed and diluted, and subject to the vagaries of distribution discussed above. While differential block in FPBs has yet to sensory receptors are served by different afferent fiber types, and the susceptibility of these fibers to local anesthetic conduction block varies.<sup>55</sup> In general, nociception (transmitted by A-delta and C-fibers) is blocked ahead of light touch, pressure, and motor function. The small myelinated fibers of A-delta nociceptors responsible for the transmission of 'fast' or 'first pain'56 (eg, pinprick) are more susceptible to conduction blockade than larger myelinated A-beta and A-alpha fibers which are responsible for mechanosensation and proprioception, respectively.<sup>57</sup> The smallest unmyelinated C-fibers implicated in temperature sensation and 'slow' or 'second pain'56 have a more nuanced response. Studies have shown that they are less susceptible to blockade by lidocaine compared with A-fibers.<sup>57</sup> However, bupivacaine and ropivacaine (the agents employed most often in FPBs) consistently display preferential blockade of C-fibers versus A-delta fibers versus A-beta fibers (in that order) in both preclinical and clinical studies.<sup>52,58,59</sup> This difference is attributed to the higher pKa and lipid solubility of bupivacaine and ropivacaine compared with lidocaine, which facilitates intraneural diffusion and ion channel blockade. Susceptibility to conduction block is also enhanced in neurons that are actively firing, as might be the case for nociceptors in ongoing pain states. This is due to the increased affinity and binding of local anesthetic for open sodium channels, a phenomenon known as use-dependent block<sup>60</sup> and one that is more marked in C-fibers.<sup>59</sup>

be systematically investigated, studies have nevertheless shown

### Sympathetic innervation and visceral pain

In the specific case of the quadratus lumborum block, it has been speculated that local anesthetic blockade of the sympathetic innervation of the thoracolumbar fascia enveloping the quadratus lumborum muscle may contribute to analgesia in some undefined way.<sup>61</sup> Here, however, we are unable to formulate a coherent or logical scientific explanation to support this argument. We believe the notion that sympathetic innervation plays an important role in pain or FPB analgesia is misplaced, and its origins can be traced to two main sources.

One is the condition formerly known as reflex sympathetic dystrophy, so named because of the association of neuropathic pain of the extremities with clinical features of sympathetic dysfunction. The name was revised to complex regional pain syndrome (CRPS) in part because the pathophysiology encompasses more than just autonomic dysregulation and sensitivity to catecholamines.<sup>62 63</sup> Sympathetic blocks, in fact, are not always effective in CRPS.<sup>64</sup> More importantly with regard to quadratus lumborum or erector spinae plane (ESP) blocks, any effect resulting from blockade of sympathetic nerve endings in the thoracolumbar fascia would apply only to pain emanating from the fascia itself (ie, back pain).

The second is the misconception that visceral pain is mediated by autonomic neurons.<sup>65</sup> In reality, sensory afferent neurons from thoracic and abdominal viscera are functionally separate from the sympathetic and parasympathetic efferents.<sup>66 67</sup> Sensory afferents synapse with second-order neurons in the dorsal horn, whereas sympathetic efferents originate in the ventral horn, and each follows different supraspinal pathways. They both, however, share the same anatomical pathway through the peripheral nervous system—sensory and sympathetic neurons travel through the same ganglia, plexuses and nerves (figure 5). As a result, although 'sympathetic' blocks targeting



**Figure 5** Simplified illustration of the visceral and sympathetic nervous system. Cell bodies of sympathetic neurons (green) are located in the anterolateral horn of T1–L2 spinal cord segments. Efferent fibers (cholinergic) pass by way of the ventral root to a white ramus communicans and then to the paravertebral sympathetic ganglia. They continue via splanchnic nerves (greater, lesser, and least) to prevertebral ganglia (eg, celiac ganglia). From here, multiple branches form autonomic plexuses (eg, celiac plexus) that supply terminal efferent fibers to the viscera. Adrenergic vasomotor efferents also leave the sympathetic ganglia to innervate blood vessels. Sensory afferent neurons from the viscera (blue) travel in the reverse direction along the same pathway as sympathetic efferent neurons but are functionally separate. The visceral sensory neurons enter the spinal nerve via white rami communicantes and converge with somatic sensory neurons. They both project onto second-order neurons in the dorsal horn of the spinal cord, and this viscerosomatic convergence is responsible for the phenomenon of referred pain. Visceral pain sensation may be blocked at the level of the celiac ganglion or plexus, or at the level of the spinal nerve and cord. However, blocking the latter site will also interrupt motor and somatic sensory function, which is generally undesirable. DRG, dorsal root ganglion. (Adapted from KJ Chin Medicine Professional Corporation)

the intra-abdominal autonomic plexuses are used to successfully treat visceral pain, their therapeutic effect is achieved by blockade of the sensory afferents and blockade of autonomic efferents is responsible primarily for side effects (eg, diarrhea, hypotension).

For these reasons, blockade of sympathetic nerve endings within the thoracolumbar fascia thus seems implausible as a mechanism for analgesia of the thoracoabdominal wall and viscera provided by quadratus lumborum or ESP blocks.

# Local analgesic effect mediated by spread into adjacent tissue compartments

Certain FPBs are also purported to exert an analgesic effect via local anesthetic penetration into muscle and tissue compartments adjacent to the fascial plane of injection. These include the quadratus lumborum block,<sup>61 68</sup> and paraspinal blocks such as the ESP, midpoint transverse process to pleura (MTP), and retrolaminar block.<sup>69 70</sup> The only nerves that pass through the targeted plane in these FPBs are the branches of dorsal rami of spinal nerves, which innervate the posterior torso. Yet there is a substantial body of evidence from clinical trials showing that they provide effective thoracoabdominal analgesia, which from a mechanistic point of view must imply that local anesthetic is acting at sites other than the plane of injection. This could be mediated in part by a systemic effect from vascular absorption (discussed further below), but the main assertion is that there is local anesthetic spread into the thoracic paravertebral space

where it acts on the ventral rami of spinal nerves. This has been demonstrated in anatomical and clinical studies (summarized in recent review articles<sup>61 71</sup>) but it remains a highly contentious point due to conflicting evidence from several cadaveric<sup>72–75</sup> and volunteer/patient studies,<sup>23 76</sup> and is largely responsible for most of the controversy that currently surrounds FPBs.

However, in the case of the ESP block at least, imaging studies in human subjects have confirmed that this is in fact possible and does occur.<sup>77 78</sup> In one study, MRI scans performed 1 hour after a T10 ESP injection in six patients with chronic abdominal pain clearly demonstrated the presence of injectate within the thoracic paravertebral and proximal intercostal spaces (figure 6). This was accompanied by complete resolution of pain in all subjects and discernible sensory loss over the anterior abdominal wall.<sup>78</sup> It is likely that the intertransverse connective tissue forming the posterior boundary of the paravertebral space largely impedes bulk flow of local anesthetic injected into the ESP, which would explain why Visoiu and Scholz failed to visualize filling of the paravertebral space on thoracoscopy during the injection phase.<sup>79</sup> However, local anesthetic can diffuse across this collagenous barrier to eventually exert a clinical effect on the spinal nerve rami and roots, resulting in a gradual onset and progression of analgesia and sensory block over time.79 80 There may also be a small amount of bulk flow through the macroscopic openings in this connective tissue layer that transmit perforating vessels and nerves.<sup>81</sup> It is likely that only a fraction of the total volume of injected local anesthetic reaches the thoracic



Figure 6 MRI of the spine showing injectate spread 1 hour after injection of 30 mL of local anesthetic and gadolinium contrast at the T10 transverse process in a patient with chronic abdominopelvic pain. (A) Parasagittal view showing spread of injectate (white line arrows) to the erector spinae muscles (\*), paravertebral space (bold arrow), and neural foramina (arrowheads). The facet joint and the inferior articular process are indicated by a black arrow and white asterisk, respectively. (B) Axial view at the level of the T11 vertebra. Injectate (line arrows) has penetrated throughout the erector spinae muscle (black asterisks). The arrowhead indicates the intervertebral neural foramen, where the dorsal root ganglion (DRG) of the spinal nerve is located. The inferior articular process is indicated by a white asterisk. (C) Another parasagittal view showing injectate within the posterior epidural space (line arrows). (D) Axial view at the level of the T10 vertebra. Injectate has spread to the intercostal space (line arrows). The neural foramen (arrowhead), paravertebral space (bold arrow), erector spinae muscle (black asterisks), and inferior articular process (white asterisk) are indicated. (adapted from Schwartzmann et al<sup>78</sup> with permission from Philip Peng **Educational Series**)

paravertebral space and ventral rami, which may explain the patchy and variable nature of cutaneous sensory block that has been reported. Nevertheless, given the preferential blockade of C-fibers by bupivacaine and ropivacaine,<sup>52,58,59</sup> this may be sufficient to provide a degree of clinically meaningful analgesia. These considerations would apply to the MTP and retrolaminar block as well.

A similar, though less vociferous, controversy applies to the role of the serratus anterior plane block in thoracic surgery and blunt trauma. Its clinical efficacy has been demonstrated in multiple studies<sup>3</sup> despite cadaveric evidence that local anesthetic spread is confined to lateral cutaneous nerves and does not reach the intercostal space and nerves.<sup>82</sup> One explanation is that physical disruption of normal tissue architecture following trauma promotes local anesthetic penetration and spread through investing fascia to deeper structures and the intercostal space, as suggested by a cadaveric model of serratus anterior plane blocks in rib fractures.<sup>83</sup> Another is the diffusion of local anesthetic into the injured chest wall muscles to block nociceptive nerve endings.

The evidence base for thoracic paravertebral spread in quadratus lumborum blocks is admittedly smaller and more equivocal at this time. Local anesthetic must physically travel over a greater distance to reach this space, and this was not borne out in a recent imaging study of injectate spread in patients.<sup>76</sup> It may exert much of its effect instead through blockade of branches

of L1 and T12 nerves, which is consistent with clinical studies demonstrating efficacy primarily for lower abdominal and hip surgery.<sup>84 85</sup> Nevertheless, sensory changes consistent with low thoracic paravertebral spread have been demonstrated in volunteers<sup>22</sup> and patients.<sup>86</sup> Furthermore, quadratus lumborum blocks are a heterogenous group of techniques, and it is likely that the pattern and extent of spread will vary with the specific approach used.<sup>22 76 87</sup> More research is needed to clarify these issues.

# How much local anesthetic is required for neural conduction blockade?

It is clear from the preceding discussion that any local effect of FPBs in blocking neural conduction is predicated on dispersion of local anesthetic over relatively large distances to reach target nerves. Logically speaking, the greater the distance between a target nerve and site of injection, the smaller the mass of drug that will reach it, and thus a corresponding diminution in effect can be expected. The question is: at what point does this cease to be clinically meaningful? In most peripheral nerve blocks, only a minor fraction of injected local anesthetic is responsible for axonal conduction block,<sup>88</sup> with the majority being absorbed into the vascular system over time.<sup>60</sup> The perineural concentrations of lidocaine and bupivacaine required to achieve tonic block of action potential propagation are anywhere from 1/5th to 1/80th of typically injected concentrations of 2% (approximately 70 mM) and 0.25% (approximately 7.7 mM), respectively<sup>55 89</sup> It is therefore plausible that clinically relevant axonal conduction blockade is occurring even at the fringes of local anesthetic spread in FPBs, although the reduced concentration gradient may mean that diffusion speed and onset times will be correspondingly slower, and offset possibly earlier. One implication of this is that more concentrated local anesthetic solutions might contribute to better postoperative analgesia, as shown in one randomized controlled trial comparing equal volumes of 0.375% and 0.25% bupivacaine in ESP block for breast surgery.90 On the other hand, no difference was observed between 0.25% and 0.125% bupivacaine when used in TAP block for open inguinal hernia repair surgery,<sup>91</sup> so this remains an area for further investigation.

### Analgesia mediated by a systemic effect of local anesthetics

The other major theory that has been advanced to reconcile the analgesia provided by FPBs with the relative lack of outward signs of conventional neural blockade is a systemic effect that follows vascular absorption of local anesthetic. On the surface, this seems intuitive given the large local anesthetic volumes used in FPBs, and the relatively widespread use of intraoperative intravenous lidocaine infusion (IVLI) in improving postoperative analgesia and recovery. However, this theory warrants more careful consideration, not least because the analgesic efficacy of IVLI is itself somewhat controversial.

### Analgesic efficacy and mechanisms of action of IVLI

A recent Cochrane review update acknowledged that while IVLI does reduce early postoperative (1–4 hours) pain scores and opioid consumption, the authors were guarded in their conclusions about the overall clinical significance of the benefits attributed to IVLI.<sup>92</sup> The analgesic effect is more marked in some surgery types and pain syndromes than others,<sup>92,93</sup> and may be due to differences in the pathogenesis of pain (eg, inflammatory vs neuropathic, visceral vs somatic) and thus the impact that can be expected from IVLI. It is speculated that prolonged pain relief following peripheral nerve blockade in chronic pain can also be attributed, at least in part, to central analgesic local anesthetic

action,<sup>94</sup> but this supposition is based largely on pharmacological principles and laboratory studies.

Multiple biologically plausible molecular mechanisms of action have been identified by in vitro and in vivo studies<sup>95-98</sup>; although it must be noted that not all of these occur at the plasma concentrations associated with therapeutic IVLI (1-5 mcg/mL).95 These mechanisms have been comprehensively reviewed elsewhere,<sup>95 96 99</sup> but in brief, lidocaine interacts with voltage-gated ion channels (eg, sodium, potassium, and hyperpolarizationactivated cyclic nucleotide-gated (HCN)<sup>97 98</sup> channels) to modulate action potential generation, depolarization-dependent neurotransmitter release, and oscillatory neuronal activity, and interacts with ligand-gated ion channels (eg, transient receptor protein and N-methyl-D-aspartate (NMDA) receptors) as well as G protein-coupled receptors such as nicotinic and muscarinic acetylcholine receptors. These interactions can potentially modulate the activity of nociceptive pathways at several different sites. In the periphery, plasmaborne lidocaine could block action potential generation or propagation at nerve endings and axons, as occurs with intravenous regional anesthesia. The concentrations achieved with IVLI are insufficient to achieve normal conduction blockade<sup>100</sup> but may be sufficient to inhibit the ectopic discharges associated with injured axons.<sup>95</sup> The peripheral contribution to analgesia may also be mediated by an anti-inflammatory action related to inhibition of neutrophil chemotaxis and priming.<sup>41 42</sup> An additional important site of action for IVLI may be in the central nervous system.<sup>101</sup> In the dorsal horn of the spinal cord, lidocaine blocks the depolarization-dependent release of neurotransmitters at presynaptic terminals, and through effects on glutaminergic (NMDA) and G protein-coupled receptors may inhibit the central sensitization that contributes to secondary hyperalgesia in acute postoperative pain.<sup>102</sup> Supraspinal mechanisms of analgesia include blockade of HCN channels which are responsible for the hyperpolarization-activated mixed cation current,  $I_{\rm b}$  or 'h' current.<sup>103</sup> In the central nervous system,  $I_{\rm b}$  serves important 'pacemaker' functions in the generation of neuronal oscillations associated with different conscious states as well as in the determination of different action potential firing modes. The ventrobasal thalamus, which is particularly rich in HCN channels, functions as a primary relay station for somatosensory and nociceptive transmission,<sup>104</sup> and has a central role in incisional hyperalgesia.<sup>105</sup> Systemic lidocaine at therapeutic concentrations inhibits the  $I_{\rm L}$  current in thalamocortical neurons<sup>97</sup> and this may contribute to the reduced perception of painful stimuli.

### Are the systemic effects of long-acting local anesthetics similar to that of lidocaine?

Two questions must be asked before the analgesic mechanisms of IVLI can be extrapolated to FPBs. The first is whether we can expect the other amide local anesthetics to have a similar systemic analgesic effect as lidocaine, considering that bupivacaine and ropivacaine are almost always employed in FPBs. Their toxicity profile precludes therapeutic studies of intravenous infusion and the nearest parallel in clinical practice is the successful use of these drugs in intravenous regional anesthesia.<sup>106 107</sup> It is of note, however, that this reflects only peripheral, and not central mechanisms of actions. Unlike lidocaine, bupivacaine and ropivacaine are chiral molecules, and stereoselectivity for sodium and potassium channels has been demonstrated, with levorotatory isomers exhibiting significantly lower affinity.<sup>108</sup> Nevertheless, at equipotent doses, any ion channel-mediated central analgesic effects are expected to be similar. Non-stereoselective interactions at

cholinergic, serotoninergic, and NMDA receptors have also been demonstrated,<sup>109</sup> <sup>110</sup> which support modulation of nociceptive signaling at the level of dorsal horn neurons. There also appear to be minimal interdrug differences in the inhibitory effects of local anesthetics on neutrophil function and the immune response, indicating that they have similar anti-inflammatory effects.<sup>43</sup> <sup>111</sup> <sup>112</sup> At this time, it is therefore reasonable to expect that bupivacaine and ropivacaine will exert systemic analgesic effects comparable to that of lidocaine.

### Local anesthetic plasma concentration following FPBs

The second question is whether FPBs achieve and sustain clinically relevant plasma concentrations of local anesthetic. In general, changes in plasma concentration follow a biphasic pattern/profile with a fast phase of redistribution that leads to an early peak concentration (Cmax) and then a slower phase of elimination.<sup>113</sup> The elimination half life is prolonged in the elderly<sup>114</sup> and obese,<sup>115</sup> slowing the decline in plasma concentration. The Cmax following FPBs is proportional to the dose administered.<sup>113</sup> Bilateral TAP block with 400 mg lidocaine (average dose by body weight of 7.3 mg/kg) resulted in Cmax ranging from 2.7 to 5.5 mcg/mL (mean of 3.6 mcg/mL) and mean plasma concentration at 2 hours of approximately 2 mcg/ mL, which is within the range of 1-5 mcg/mL associated with therapeutic IVLI. On the other hand, a unilateral ESP block with lidocaine 3.5 mg/kg (175–350 mg) produced Cmax ranging from 1.2 to 3.8 mcg/mL (mean of 2.6 mcg/mL), but within 2 hours, the mean plasma concentration had fallen below 1 mcg/mL.<sup>116</sup>

It is unclear what minimum duration of IVLI exposure is required for durable physiological changes in pain transmission, transduction, and modulation. Nevertheless, in a recent metaanalysis of IVLI, the minimum average duration of infusion was 60 min, and in most studies exceeded 2 hours. Single-injection FPBs using local anesthetic doses close to maximum recommended limits are therefore capable of producing extended plasma concentration profiles similar to that of intraoperative IVLI. If a continuous local anesthetic infusion is initiated, this will prevent the decline in total plasma concentration, and in fact a gradual increase over time is observed.<sup>115</sup> <sup>117</sup> This increase is balanced out by postoperative increases in the acute-phase protein alpha-1 acid glycoprotein, which has a high binding affinity for local anesthetic molecules, and the net result is that free local anesthetic plasma concentrations remain relatively constant.<sup>117 118</sup>

Several other factors must be considered apart from dose. Systemic absorption and actual plasma concentration achieved is dependent on physicochemical characteristics of the drug (lipophilicity, protein binding, pKa) which determine binding to the tissues at the site of injection, as well as the composition and vascularity of the site of injection. The plasma concentration achieved by a given dose will therefore vary for different local anesthetics and different FPBs.<sup>113</sup> There is also a degree of interindividual variability, with threefold variations observed in Cmax and area under the concentration-time curves (figure 7).<sup>115</sup> 116 119 Finally, any distant effect site tissue concentrations of local anesthetics will also vary depending on both free plasma concentration and many of the same factors that determine vascular uptake from the injection site.<sup>29</sup>

### Relative contributions of local and systemic effects to analgesia in FPBs

At the current time, it is difficult to disentangle the relative contributions of neural conduction blockade from the systemic



**Figure 7** Arterial and venous plasma concentrations of levobupivacaine over time following a unilateral lateral transversus abdominis plane (TAP) block with 20 mL 0.25% levobupivacaine (50 mg), with and without the addition of 5 mcg/mL epinephrine (E). The median values are indicated by the thicker bold lines; other lines show individual measurements in each human volunteer. Note the high degree of interindividual variability in concentration values, especially where epinephrine was not added (dashed lines). (adapted from Corvetto *et al*<sup>119</sup> with permission)

effect of local anesthetics, and to assign primacy to one or the other. Their relative importance may depend on the etiology of the pain syndrome being treated, as well as the specific technique of FPB being used. FPBs that target peripheral nerves in the thoracic or abdominal wall will not block visceral nociceptive pathways, and any visceral analgesia ascribed to them may be due to a systemic effect instead.<sup>120</sup> Systemic absorption may also be more significant in scenarios where higher doses or continuous infusions are administered that promote and prolong higher plasma concentrations, or where the neural targets available for direct action are dispersed further away from the site of injection. As an illustration, randomized controlled trials have compared the analgesic efficacy of IVLI and FPBs (TAP<sup>121</sup> and quadratus lumborum block<sup>122</sup>) in laparoscopic abdominal surgery and found no difference. At the same time, the analgesic efficacy of chest wall FPBs in breast surgery (where unilateral blocks and lower doses are the rule rather than the exception) has been clearly demonstrated<sup>1 2</sup>; whereas no such effect has been observed with IVLI.<sup>123–125</sup> One possible explanation is that there is a much larger visceral component of pain in laparoscopic abdominal surgery that is not impacted by sensory blockade of the abdominal wall, whereas postoperative pain following breast surgery largely emanates from superficial tissues that are readily anesthetized by FPBs. Abdominal surgery also generally requires bilateral, rather than unilateral, blocks, and the larger local anesthetic dose may contribute to a greater systemic effect.

### Clinical implications and future directions for research

The weight of current clinical evidence supports a beneficial analgesic effect for FPBs in various pain syndromes.<sup>1-10</sup> It is increasingly clear, however, that the magnitude of this benefit in individual patients can be unpredictable. Much of this can be ascribed to the variability in technical performance, in local anesthetic spread within the fascial plane, and in systemic uptake into the vascular system and distant tissues, all of which ultimately affect the local anesthetic concentration and mass available to act at therapeutic target sites. The factors underlying interindividual variability are not completely understood and there are as yet no definitive data on how to improve the consistency of analgesia with FPBs. Nevertheless, based on the preceding discussion, several logical strategies may be derived that are worthy of further systematic investigation.

The first is to deposit local anesthetic closer to the target structures of interest wherever possible. As an example, rectus sheath blocks or subcostal TAP blocks are clearly better choices than lateral TAP blocks in supraumbilical midline abdominal incisions.<sup>126</sup> Careful consideration should also be given to local anesthetic dosing. While higher volumes will theoretically promote bulk flow and fascial plane spread over a greater area, this does not always hold true<sup>16</sup> and it may be more important to divide this higher volume between multiple injection sites rather than at a single one.<sup>16 127 128</sup> Manipulating local anesthetic concentrations could potentially influence diffusion and the pharmacodynamics of conduction block, but the evidence for benefit is presently equivocal.<sup>90 91</sup> Delivering a higher overall mass of local anesthetic will also increase plasma concentrations and any systemic analgesic effect. However, it goes without saying that preventing local anesthetic systemic toxicity should still be the foremost priority, and maximum recommended doses must be strictly adhered to. The addition of epinephrine will reduce peak plasma concentrations and is recommended.<sup>129</sup> It should be noted that most of the available pharmacokinetic data pertain to the TAP block and more studies of the other FPBs are required. As with peripheral nerve blockade, incorporating other local anesthetic additives such as dexamethasone<sup>130</sup> 131 and dexmedetomidine<sup>132-135</sup> may enhance the analgesic effect of single-injection FPBs; but it is not clear as yet if this is primarily a systemic effect, in which case intravenous administration should be equally effective. Finally, continuous catheter techniques of FPB may be beneficial in maintaining therapeutic local anesthetic concentrations in both the fascial plane and systemic circulation, and might serve to prolong both local conduction block and systemic analgesia. Although an intermittent bolus dosing regimen would seem to be an intuitive choice over continuous infusion in terms of promoting fascial plane spread, the limited evidence currently available suggests that analgesic efficacy is similar.<sup>136–138</sup> Further research is necessary to reach a definitive answer.

#### CONCLUSION

This article represents our subjective attempt at synthesizing the clinical evidence for the mechanisms of analgesia provided by FPBs, and at reconciling conflicting opinions through logical thought experiments based on this evidence and accepted scientific principles and our current understanding of the basic science of nociception and local anesthetic pharmacology. To this end,

Table 1         The current state of knowledge on mechanisms of analgesia in fascial plane blocks	
What is known	What is uncertain
<ul> <li>Nerves run in and through fascial planes.</li> <li>LA spreads in fascial planes and can achieve sufficiently high concentrations for neural conduction blockade.</li> <li>LA can spread out of fascial planes into adjacent tissue compartments.</li> <li>Neural conduction block requires only relatively small amounts of LA.</li> <li>Different nerve fiber types have different sensitivities to LA.</li> <li>Clinically significant blockade of nociceptive transmission can be achieved without complete sensory or motor blockade.</li> </ul>	<ul> <li>The degree to which cadaveric studies of injectate spread correspond to injectate spread and clinical effect in living human subjects.</li> <li>Determinants of LA spread within and beyond fascial planes in individual patients.</li> <li>Determinants of vascular absorption and LA plasma concentration in individual patients.</li> <li>The exact influence of volume, concentration and mass of LA on clinical efficacy of FPBs.</li> <li>The extent to which FPBs block nociception from deeper musculoskeletal tissues.</li> <li>The contribution of motor nerve blockade to analgesia in certain pain syndromes.</li> <li>If equipotent doses of intravenous bupivacaine and ropivacaine have similar systemic analgesic effects</li> </ul>
<ul> <li>FPBs do not always result in expected patterns of cutaneous sensory blockade.</li> <li>Pain from surgery or trauma originates from cutaneous tissues and deeper tissues, including murcle connection tircup and heart to be a sense to be always and the sense of the</li></ul>	<ul> <li>to intravenous lidocaine.</li> <li>If the plasma concentrations of bupivacaine and ropivacaine resulting from FPBs are sufficient to produce clinically configer a curtary is applaced.</li> </ul>
<ul> <li>FPBs produce peak plasma lidocaine concentrations in the range associated with therapeutic intravenous lidocaine infusion.</li> </ul>	<ul> <li>The molecular mechanisms of LA action that are directly relevant to the clinical analgesia associated with FPBs and different pain syndromes.</li> </ul>
<ul> <li>Bupivacaine, ropivacaine, and lidocaine have broadly similar mechanisms of action and recentor interactions</li> </ul>	<ul> <li>The relative contribution of localized and systemic effects of LA to clinical analgesia in FPBs.</li> <li>If LA additives in FPBs consistently improve clinical analgesia and whether this is primarily mediated by</li> </ul>

a local or systemic effect.

FPB, fascial plane block; LA, local anesthetic.

we have summarized the firmly established facts and the assumptions that await definitive proof (table 1). At this time, the two most plausible mechanisms of analgesia underlying FPBs are (1) a localized action on nociceptors and neurons in the vicinity of the site of injection within the fascial plane, mediated by the processes of bulk flow and diffusion; and (2) vascular absorption of local anesthetic leading to a systemic effect similar to that described for IVLI. The relative importance of their contribution remains uncertain. In the mean time, as we await the results of further research, the pragmatic approach is to accept that analgesic efficacy may be unpredictable in any given individual, and thus to always use FPBs as part of a multimodal analgesic strategy. On the other hand, their favorable benefit-risk profile and relative ease of performance make them well suited to incorporation into clinical pathways of enhanced recovery and a more broad-based model of care.

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