Pulling and Tugging on the Retina: Mechanical Impact of Glaucoma Beyond the Optic Nerve Head

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Optical coherence tomography (OCT) has become an integral component of clinical assessment for glaucoma diagnosis and management. Its steady growth into clinical practice reflects the fact that OCT enhances clinical examination by providing high-resolution cross-sectional images of retinal and optic nerve head (ONH) anatomy as well as rapid, reliable quantitative measurements of the tissue layers damaged by glaucoma, such as the peripapillary retinal nerve fiber layer (RNFL), macular inner retinal layers, and ONH neuro-retinal rim. Beyond these now standard measures, however, a series of recent reports demonstrates that OCT also reveals additional retinal structural abnormalities associated with glaucoma that were previously not known to be part of the constellation of its clinical signs. The purpose of this presentation is to review the OCT findings described in these reports and to propose a framework that could explain why they are related and occur more frequently in glaucoma.

**Hypodense Holes** of the RNFL

In 2011, Xin et al. showed that OCT circumpapillary B-scans of glaucomatous eyes frequently contained “holes” within the RNFL. These holes appeared as small round or oval regions of very low or absent (“hypodense”) reflectance, conspicuous in contrast to the normally strong reflectance produced by axons within the RNFL (Figs. 1A, 1B). The study by Xin et al. included 208 eyes of 110 patients with glaucomatous optic neuropathy and 45 eyes of 45 healthy controls. Holes within the RNFL were found in 33 (16%) of the glaucomatous eyes (or in 28 of the patients, 25%) but in none of the healthy control eyes. Holes were nearly always located immediately adjacent to a major retinal blood vessel near the superior or inferior pole of the optic disc, most commonly one of the branches comprising the temporal arcades.

In addition to circumpapillary B-scans, Xin et al. also used raster (“cube”) scan patterns to show how holes appearing on a circumpapillary B-scan often represented just one slice through a tubular shaped void whose long axis followed an arcuate RNFL bundle path (Figs. 1E, 1F). In some cases, a tubular void appeared to collapse at a given eccentricity from the optic disc, resulting in the appearance of a fissure of the anterior (vitread) RNFL. These structural defects were associated with localized visual field (VF) scotomas in some eyes, and many of the example B-scans provided in the paper show that the holes were also associated with RNFL defects. Collectively, these findings led the authors to hypothesize: “that a loss of local axons may create a local mechanical force that pulls axons away from the nearest vessel. Alternatively, and probably less likely because vessels are known to constrict in patients with glaucoma, it may be the vessel itself is being pulled away from the axons.”

Further evidence that these structural voids occur in conjunction with RNFL defects came from another study by the same group, which demonstrated that glaucomatous RNFL defects detected on OCT circumpapillary B-scans are most common near the major blood vessel branches in the inferotemporal, superotemporal, and superonasal sectors, but much less commonly the inferonasal sector, which matches...
closely the spatial distribution found by Xin et al. for holes of the RNFL.

PARAVASCULAR DEFECTS

Muraoka et al. in 2015 used OCT to carefully characterize a spectrum of “paravascular inner retinal defects” (PIRDs) found in 41 eyes of 21 patients, most commonly along the retinal veins of the superior temporal arcade. Of these 41 eyes, 37 (90%) were myopic, 21 (51%) had high myopia, and 21 (51%) had macula epiretinal membrane (ERM), but only 6 of the latter 21 eyes had high myopia. Thus, Muraoka et al. concluded that PIRDs primarily occur in eyes with high myopia or ERM and proposed that mechanical traction due to axial elongation in myopia, or to contractile forces exerted by ERM, cause inner retinal tissue to tear apart from the vessels. Since most eyes with PIRD (91%) had no OCT evidence of vitreous adhesion onto the inner retinal surface, the tractional forces involved are more likely acting laterally. Hwang et al. reported similar findings in myopia and ERM and also proposed lateral traction as an explanation.

Having appreciated the similarity of the OCT findings reported by Muraoka et al. in myopia and ERM to the previous findings reported by Xin et al. in glaucoma, Hood et al. then conducted a follow-up study to extend their earlier analysis of hypodense holes. Using wide-field swept source OCT scans obtained in 19 eyes of 15 glaucoma patients originally identified as having hypodense holes on OCT circumpapillary B-scans, Hood et al. measured the length of these paravascular defects and evaluated its relationship to high myopia, ERM, and arcuate RNFL bundle defects. Hood et al. reported that 13 of the 19 paravascular defects were consistent with “PIRD” as described by Muraoka et al. Nine of those 13 (69%) had high myopia and/or ERM and three of those also had a glaucomatous arcuate defect associated with the PIRD-like paravascular defect. The other 6 of 19 had shorter paravascular defects, which appear as a spherical “hole” rather than an elongated tubular defect, and which were all associated with an RNFL arcuate bundle defect. It will be

FIGURE 1. Example of hypodense holes and paravascular defects. (A) Scanning laser ophthalmoscope (SLO) infrared reflectance image of an eye with early glaucoma [Caucasian female, age 66, VF MD of -0.2 dB, pattern standard deviation (PSD) of 1.7 dB, borderline glaucoma hemifield test, and circumpapillary RNFL thickness of 78.1 μm]; the green circle indicates the position of the 12-degree diameter circumpapillary B-scan shown to the right. (B) Circumpapillary B-scan exhibits small defects between the inferior branch vein and artery (red arrows), similar in appearance to the “hypodense holes” reported by Xin et al. (see their figures 1 and 2, for example). (C) SLO image with thin green lines indicating the position of 24 radial B-scans, each spanning 15-degrees and centered on the ONH; the bold green arrow indicates the position of the B-scan shown to the right. (D) Vertically oriented B-scan beginning near the same location with “hypodense holes” shown in B reveals a wider split between the RNFL and GCL that could be interpreted as a peripapillary retinoschisis (red arrow). (E) SLO image with thin green lines indicating the position of 61 B-scans comprising a “posterior pole” raster pattern. A red dot is placed adjacent to the inferior branch vein on every second B-scan beginning near the position shown by red arrows in panels B and D, extending peripherally. (F) These eight inset panels show the portion of each corresponding B-scan along the course shown by the red dots in panel E along the course of the inferior branch vein. These demonstrate that the “hypodense holes” appearing in the circumpapillary B-scan of panels A and B are one slice through a set of tubular-shaped “paravascular defects.”
interesting to learn the results of longitudinal studies that follow the evolution of paravascular defects, holes, and PIRDs, particularly to determine if smaller, shorter holes eventually develop into PIRDs and under what circumstances. Meanwhile, it is clear that substantial overlap exists between the paravascular defects found in high myopia, ERM, and glaucoma, which suggests that they may all have in common some degree of lateral traction differentially affecting retinal vessels and neural retina. Future studies are needed to test this hypothesis directly. The possibility that older age increases the risk of developing such conditions also needs to be addressed.

**PERIPAPILLARY RETINOSCHISIS**

Recent studies using OCT have also revealed that peripapillary retinoschisis (PPRS; Fig. 2) is associated with glaucoma, occurring over 10 times more frequently in glaucoma patients than controls, often along an existing RNFL bundle defect. Additionally, a recent study from our group found that PPRS in glaucoma was associated with a more rapid rate of overall progression, measured both by circumpapillary RNFL thickness and by standard VF mean deviation (MD), compared with glaucomatous control eyes that did not have PPRS. Based on the findings reported in our study and by others, we postulated that lateral mechanical forces likely contribute to the development of PPRS in glaucoma (perhaps in addition to vitreoretinal adhesions). We noted, as others have too, that PPRS in glaucoma tends to occur more frequently in the superior and inferior sectors (superior about twice as often as inferior) and that all instances of PPRS included at least one major blood vessel within the affected area. We also characterized in that report OCT signs of Müller cell reactive gliosis, although it is unclear whether Müller cell changes represent only a response to the schisis or an earlier aspect of its pathogenesis. These OCT signs included hyperreflectivity of the putative Müller cell inner processes and apparent signal attenuation posterior to the inner processes, which may reflect increased scatter due to elaboration of Müller cell cytoskeletal structure and/or altered optical wave-guide behavior.

**“MICROCYSTIC MACULAR EDEMA” (INNER NUCLEAR LAYER PSEUDO-CYSTS)**

Another retinal structural abnormality revealed by OCT to be associated with glaucoma is the presence of pseudo-cysts (lacunae or vacuolar voids) within the inner nuclear layer (INL; Fig. 3), a condition often referred to as “microcystic macular edema” (or “microcystic macular degeneration”). These lesions are not specific to glaucoma, as the same findings have been reported in a wide array of other optic neuropathies with varying etiology. Several mechanisms have been proposed to explain the development of INL pseudo-cysts, including retinal inflammation, breakdown of the blood-retinal barrier, and trans-synaptic degeneration of neurons within the INL and/or traction by the vitreous. However, none of these have been established, nor have any been able to account for the complete spectrum of findings observed in these cases (discussed below).
Two recent OCT studies have estimated the frequency of “microcystic macular edema” (i.e., finding pseudo-cysts within the INL) in glaucoma and documented the clinical characteristics of those cases. Brazerol et al.21 evaluated 218 consecutive glaucoma patients and observed INL microcysts in eight eyes (2.8%) of eight patients (5.7%). After excluding the eyes with microcysts and selecting one eye from each of the remaining 210 patients for analysis, Brazerol et al.21 demonstrated that the combined macular ganglion cell layer/inner plexiform layer (GCL/IPL) thickness was strongly correlated with peripapillary RNFL thickness.21 This implies that glaucomatous damage causes proportional thinning of both anatomical features. However, in the same 210 glaucomatous eyes without microcysts, the thickness of the combined macular INL/outer plexiform layer (INL/OPL) was inversely proportional to the peripapillary RNFL.21 By extension, this indicates that the INL/OPL thickness is also inversely proportional to the degree of macular inner retinal loss and peripapillary RNFL loss, just as we had reported in a nonhuman primate model of experimental glaucoma.22 In the latter report, we proposed that the increase in outer retinal thickness was likely due to incomplete collapse of the retina following glaucomatous loss of retinal ganglion cells from the inner layers of the macula.22 Consider also that the values of peripapillary RNFL and GCL/IPL thickness reported by Brazerol et al.21 for the eight eyes with microcysts were near the lower limit of the range reported for glaucomatous eyes without microcysts (see their tables 1 and 2). These findings indicate that in glaucoma, microcysts are found only in eyes with relatively severe loss of inner retinal volume, which in turn is associated with increased outer retinal thickness. 

Hasegawa et al.25 have also carefully studied microcystic lesions of the INL in glaucoma using OCT. They reported finding microcystic INL lesions in 6.0% (13 of 217) eyes with primary open angle glaucoma.25 Their analysis revealed that the eyes with microcystic INL lesions had a more severe stage of glaucoma compared with eyes that did not and had undergone a three-fold faster rate of VF progression, on average, as determined by change in MD (dB/year).25 Their report demonstrated clearly that INL microcystic lesions were found in areas where the inner retina was severely thinned due to loss of the overlying RNFL, GCL, and much of the IPL, particularly when that region was adjacent to areas with more normal thickness such as sharply defined arcuate defects.25

**Proposed Refinement of a Mechanical Explanation for INL Pseudo-Cysts**

As mentioned above, several potential mechanisms have been proposed to explain the development of microcystic macular edema.2,14,16-20 However, none are completely satisfactory in the context of the following considerations. First, cystoid lacunae develop within the INL only where the more proximal retinal layers (RNFL, GCL, and IPL) are thickest in healthy retina, but have undergone rapid degeneration due to loss of retinal ganglion cells and their axons. This explains the distinct distribution of pseudo-cysts when they are most widespread and fulminant. In such cases, their distribution forms a ring or C-shaped pattern around the foveal pit, sparing somewhat the region under the temporal raphe.15,18,24,25 Importantly, in these cases INL pseudo-cysts do not appear everywhere that retinal ganglion cells and axons are lost, rather only where the volume of that loss is substantial, that is, precisely where the inner retina is thickest in health.13,15,18,25,26 Lujan and Horton18 argued that this distribution reflects the normally tighter adhesion of the vitreous to the internal limiting membrane (ILM) around the rim of the foveal pit. Moreover, they proposed that after substantial loss of inner retinal tissue volume occurs: “collapse of the inner nuclear layer is prevented by inwards and lateral traction exerted by the intact or partially detached posterior hyaloid membrane.” However, others have noted cases of INL pseudo-cysts in the absence of any signs of vitreoretinal adhesion and/or after complete detachment of the posterior vitreous had been established.23,24

Yet even without traction from the vitreous, the same principle proposed by Lujan and Horton18 remains valid because the ILM is likely to exert some degree of anterior force due to its lateral tension; although the ILM is thin (0.5-1.0 μm), its collagen fibrils are interwoven with the basement membrane of the Müller glia, as well as the adventitia of retinal vessels, and thus secured across the entire retina.27 Therefore, the ILM is likely to have a tent-like inertia resistant to collapse or lateral displacement, particularly when supported by healthy Müller glia.28 If the ILM is held aloft by lateral tension, Müller glia and the retinal vasculature, any severe atrophy of the inner retina, particularly if abrupt and focal, should result in forces tending to stretch the remaining retina, most likely borne by the Müller glia in that region.29

This scenario would explain why the thickness of the outer retina increases as the inner retina atrophies23,22 and is generally consistent with the ideas proposed by Lujan and Hong23 and Hasegawa et al.25 to explain development of INL pseudo-cysts even in the absence of traction by the vitreous. This implies that pseudo-cysts develop in the INL because it is being stretched, opposite the sequence common to current prevailing thought whereby the development of pseudo-cysts causes the INL to become thicker. Moreover, trans-synaptic degeneration of INL neurons would tend to cause INL thinning, not thickening. As for why pseudo-cysts develop specifically within the INL under these circumstances, it might be related to biomechanics of Müller cells, which are thought to be stiffer at their soma and relatively more pliable along their inner processes,30 thus more likely to tear apart from neighboring neuronal cell bodies within the INL and stretch the outer retina anteriorly as the inner retina atrophies.

It is also important to note here that a similar interplay of mechanical forces, along with the tolerance and response of Müller glia and their peculiar arrangement within the fovea, has been proposed to explain the development and pathological features of macular holes as well as their prognosis and potential recovery after surgical repair.31-35 Interestingly, in figure 3I of the report by Hasegawa et al.,25 there are also signs of a small paravascular defect developing adjacent to a progressive (broadening and deepening) arcuate bundle defect. This adds further circumstantial evidence that ties together the development of paravascular defects and INL pseudo-cysts: as the volume of inner retinal tissue decreases, the retina fails to collapse completely and surrounding regions are stretched, in some cases tearing apart. What differentiates eyes in which pseudo-cysts or paravascular defects develop from eyes in which they do not is likely related to the biomechanics of the ILM and Müller glia. In this regard, it is interesting that OCT may reveal signs of reactive gliosis in Müller glia characterized by increased backscatter through the inner retina and greater attenuation apparent in reflectance of outer retinal elements (see e.g., Fortune et al.,15 Gocho et al.,25 and Lujan and Horton18). For example, while the reflectivity of outer retinal bands appears hyperintense directly posterior to each INL “microcyst” (suggesting less attenuation through the cavity), the bands between the microcysts, surrounding the ring of microcysts and isolated circular portions at the base of the foveola are all hypointense.13

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WHY MIGHT THESE RETINAL OCT FINDINGS OCCUR MORE FREQUENTLY IN GLAUCOMA?

Deformation of the lamina cribrosa (LC) and peripapillary sclera, the primary load-bearing connective tissue structures of the ONH, has been for decades appreciated as a defining characteristic of glaucomatous optic neuropathy. Landmark studies connecting clinical observations to histological findings showed that the LC was increasingly compacted and bowed posteriorly as a function of disease severity. The associated distortion of its microarchitecture suggested clear hypotheses for axon injury, via direct mechanical impact (e.g., shear strain), or via potentially interactive effects on the ONH vasculature, astroglia, the extracellular matrix, and the immune system.

Today, OCT enables 3D visualization of the LC in the living eye. Clinical research studies using current commercially available OCT instrumentation have confirmed that the axial position or “depth” of the anterior LC surface is much farther posterior and more steeply curved (“bowed”) in glaucomatous eyes as compared to healthy control eyes. Note: the anterior LC surface depth, ALCSD, is typically measured relative to a reference plane such as the Bruch’s membrane (BM), its termination (BM opening [BMO]), or the choroidal-scleral interface, CSI. These LC differences measured by OCT are most apparent in glaucomatous eyes with a history of higher intraocular pressure (IOP) and for patients of relatively younger age. Recent evidence shows that greater LC depth and curvature are also predictive of faster glaucoma progression. OCT studies have confirmed and extended evidence that these LC structural differences are unique to glaucoma among optic neuropathies, particularly when matched for otherwise similar levels of VF damage and nerve fiber layer loss. Longitudinal OCT measurements reveal that some glaucomatous eyes undergo anterior, while most others undergo posterior LC displacement over time.
especially when choroidal thickness changes are accounted for by using measurements based on the CSI or BM instead of the BMO.47,57 Importantly, however, recent evidence suggests that posterior LC displacement over time carries a much worse prognostic risk for progression of VF loss.48 Experimental studies have shown that longer-term morphological alterations of the LC, including its posterior displacement, reflect a combination of plastic deformation and active remodeling of the ONH connective tissue extracellular matrix.56–61 Whereas acute deformations occurring on a shorter time scale generally represent elastic (recoverable) changes. Abrupt IOP elevation results in morphological deformation of the LC including posterior displacement of its anterior surface52;2 while lowering IOP, for example, by surgical means, results in anterior displacement and reduced curvature (less bowing).49,53–56 These more sudden shifts in the ALCSD can achieve a similar magnitude as that observed in cross-sectional and longitudinal studies, in some cases as large as hundreds of micrometers and too rapidly to represent remodeling.52,53,58 Some component of these acute changes in the anteriorsurface may reflect changes in the thickness of the LC (that is, manifest different magnitude compared to the LC posterior surface).69 However, to the extent that axon bundles are linked to the collagenous LC beams via integrins and other extracellular matrix components of the astrocytic lining between them,70 such acute positional changes of the LC would necessarily stretch axons around the rim of the ONH. The only way axons would not experience stretch is if the bundles could slide through the LC pores and/or if their soma could displace (slide) laterally within the retinal ganglion cell layer toward the ONH; both rather unlikely possibilities.70,71 Similarly, the adventitia of the major retinal blood vessels (the central retinal artery and vein and their primary branches) is linked into the LC and extracellular matrix network of the prelaminar separte,72,73,74 such that posterior LC deformation must exert forces along the retinal vasculature.

For the case of axons being stretched around the ONH rim by glaucomatous deformation and posterior LC displacement, we have proposed that such a mechanism might be contributory to the development of axonopathy,75 perhaps directly via mechanosensitive mechanisms.76 This hypothesis for axon stretch awaits testing. However, in the case of the retinal blood vessels, there already exists compelling evidence. For example, Radcliffe et al.75 demonstrated that the position of the retinal vessels near the optic disc shifted over time in 26% of glaucomatous eyes. Their study revealed a strong association between positional shifts of the retinal blood vessels and the severity of glaucoma progression.75 For example, retinal vessel positional shifts were 20 times more likely to occur in eyes with photographic evidence of ONH rim thinning over time than in eyes without rim thinning and were more common in eyes with moderate to fast rates of VF decline.75

Similarly, Kuroda et al.76 found in a study of experimental glaucoma in nonhuman primates that the first bifurcation point of the inferior and superior branches of the central retinal vein moved toward optic disc by ~100 to 200 μm, on average, and in proportion to the degree of “cupping” evident in fundus photographs. Although the findings in both of these studies represent relatively longer term changes in the position of the retinal vessels in relation to the degree of progressive glaucomatous ONH damage, which may result from remodeling within the retina, they do suggest that forces may be exerted along the retinal vessels as a result of glaucomatous ONH deformation. Additional supporting evidence was reported recently by Fazio et al.77 who found that upon acutely and independently altering IOP or cerebrospinal fluid pressure in eyes of living human organ donors, biomechanical strains within the peripapillary retina were greatest in magnitude along the vasculature as compared with the neighboring neural retina.

**Unifying Theory Proposed**

Thus, it is possible that differential shear forces arise from acute and chronic glaucomatous ONH deformation and contribute to the development of conditions observed by OCT in the retina, including hypodense holes, paravascular defects, and PPRS in glaucoma. That retinal findings such as PIRDs, inner retinal cleavage, paravascular defects, and PPRS are associated with glaucoma and high myopia (as well as with ERM), particularly near retinal blood vessels, suggests that they share a common origin: forces exerted by lateral tension, which may have differential effects (biomechanical stress and/or strain) along the vessels and adjacent neural retina. ERM and axial elongation in myopia are well known examples of conditions that may cause increased shear forces on the retina. Here we have argued that glaucomatous ONH deformation is also likely to exert shear forces on the retina. In this context, the results of another recent longitudinal myopia study are pertinent: Lee et al.78 documented a progressive nasal shift in the position of the major retinal vessel trunks within the scleral canal and over the peripapillary retina as axial length increased in progressive myopia. And a recent report by Mavrommatis et al.79 has revealed an intriguing overlap between glaucoma, ERM, and paravascular defects. In that study, Mavrommatis et al.79 showed that the frequency of ERM was substantially higher in eyes with early-stage glaucoma than in glaucoma suspect or healthy control eyes and that paravascular defects, which also occurred with higher frequency in early glaucoma, were found even in the absence of ERM or high myopia. The evidence from these recent OCT studies lends further support to the theory that glaucoma exerts lateral tension on the retina, in a manner and with similar manifestations to myopia and ERM. Indeed, the results reported by Mavrommatis et al.79 suggest that glaucoma may itself be a risk factor for development of ERM.

If the ILM is also under increased tension due to posterior deformation of the ONH tissues, it may also exacerbate the scenario outlined above as an explanation for why only some glaucomatous eyes with severe (and/or rapid, focal) loss of inner retinal volume develop pseudo-cysts within the INL, hypodense holes, paravascular defects, or PPRS (with or without traction from the vitreous). In some eyes, presumed tension acting on the ILM and glial membrane comprising the optic disc surface (the central meniscus of Kuhnt) appears to yield to progressive posterior glaucomatous deformation and detach from the underlying disc tissue and central retinal vessel trunks (Figs. 2, 3, 4). Such examples further support the suggestion that ONH deformation may exert lateral tension along the retinal surface because these tissues are normally continuous with the retinal ILM. If Müller glia sense and react to these forces,20,80 it is possible that their mechanisms for maintaining water balance and cell-to-cell adhesion become altered,43 contributing to development, persistence, or recurrence of fluid-filled voids such as pseudo-cysts, paravascular defects, and PPRS. Similarly, if Müller cells have entered a state of reactive gliosis, signs of which are known to be present in human glaucoma,42 their capacity to maintain homeostasis within the retinal environment may be further compromised, potentially contributing to worsening glaucoma.81,82 Perhaps the Müller glia hold the key to understanding the relationship between progressive glaucoma and the retinal structural defects revealed by OCT.
In order to test the hypothesis that these retinal defects develop as a result of glaucomatous ONH deformation and the differential strains it may cause throughout the peripapillary retina, it would be interesting to apply 3D strain mapping techniques to acute and longitudinal deformations captured by OCT. With the addition of adaptive-optics and MHz acquisition speeds, OCT can achieve spatial and temporal resolution capable of revealing details and dynamic activity of individual cells within the inner retina. It may someday be possible to study biomechanical strain responses at the cellular level in the living human eye.

**SUMMARY**

Several retinal conditions have been recently revealed by OCT to occur in glaucoma more frequently than in healthy eyes. Some of these conditions (such as paravascular defects and PPRS) are also known to be associated with myopia and ERM. Others such as pseudo-cysts of the INL are known to occur in a wide variety of other optic neuropathies. Yet aspects they all share in common include a strong tendency to develop in association with severe and/or rapidly progressing disease and a likelihood of involving biomechanical forces and differential tissue deformation. Müller glia are mechanosensitive and known to react to shear and axial strain, and to participate in homeostasis of water and ion flux through the retina, and to provide spring-like capability to buffer of mechanical forces. Thus, Müller cell integrity is also likely to be involved in the development and/or response to such events. OCT has also revealed that Müller cell optical properties (scatter and attenuation) appear to be altered in at least two of these retinal conditions: PPRS and pseudo-cysts of the INL. Future studies applying 3D strain mapping techniques might reveal structural changes over time (either acute or longer-term deformations) that predict the onset and location of these retinal defects and their relationship to progressive ONH deformation, RNFL, and retinal ganglion cell loss in glaucoma.

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