ORIGINAL ARTICLE

Eur. J. Anat. 23 (4): 253-259(2019)

The 3-D muscular structure of the human pancreaticobiliary junction

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SUMMARY

The musculature of the human pancreaticobiliary junction (PBJ) is implicated in several pathologies and is of significance to clinicians who perform endoscopic retrograde cholangiopancreatography (ERCP). This study sought to describe the musculature of the human PBJ by generating a three-dimensional reconstruction of histologic sections. A single pancreaticoduodenal specimen was removed en bloc from an embalmed cadaver with no pancreaticoduodenal disease. Sections were stained with Masson's trichrome and the staining pattern of muscle fibers was used to generate information regarding their location and orientation. The outline of groups of muscle fibers taken from photomicrographs of alternate thin serial sections were highlighted based upon their orientation (circular or longitudinal) and location (duodenal or papillary). Data point co-ordinates were used to create a 3-D image reconstruction.

A total of 91 composite serial cross-sections were reconstructed. Circular and longitudinal muscle fibers formed a completely investing muscle layer around both the bile and pancreatic ducts, and there was a clear distinction between the intrinsic muscles of the PBJ and those of the duodenal wall. Circular fibers were particularly dense distal to the confluence of the ducts. Longitudinal fibers were incompletely distributed around the pancreaticobiliary sphincter and did not extend to the tip of the major duodenal papilla. This model supports the well-established concept of an intrinsic pancreaticobiliary sphincter composed of circular and longitudinal muscle fibers, distinct from the surrounding duodenal muscle. Targeting the distal end of the PBJ during ERCP would only partially disrupt this muscular sphincter mechanism.

Key words: Pancreaticobiliary junction – Sphincter ampullae – 3-dimensional structure – Endoscopic – Retrograde cholangiopancreatography – Sphincterotomy

INTRODUCTION

The structure and function of the pancreaticobiliary junction (PBJ) has intrigued scientists and clinicians for centuries (Dardinski, 1935; Hand, 1963; Loukas et al., 2007). Abnormalities in structure and/or function have been implicated in several pathologies, including pancreaticobiliary malunion, sphincter of Oddi (SOD) dysfunction and recurrent acute pancreatitis (Funabiki et al., 2009; Kyanam Kabir Baig and Wilcox, 2016; MD PS and MD UN, 2016). The anatomy of the junction is especially important for clinicians who perform endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (Bosch and Pena, 2007; Yaghoobi and Romagnuolo, 2015).

The termination of the bile duct was first documented by Vesalius in 1543, and the anatomy of the musculature of the PBJ has since been the

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Submitted: 10 February, 2019. *Accepted:* 6 May, 2019.

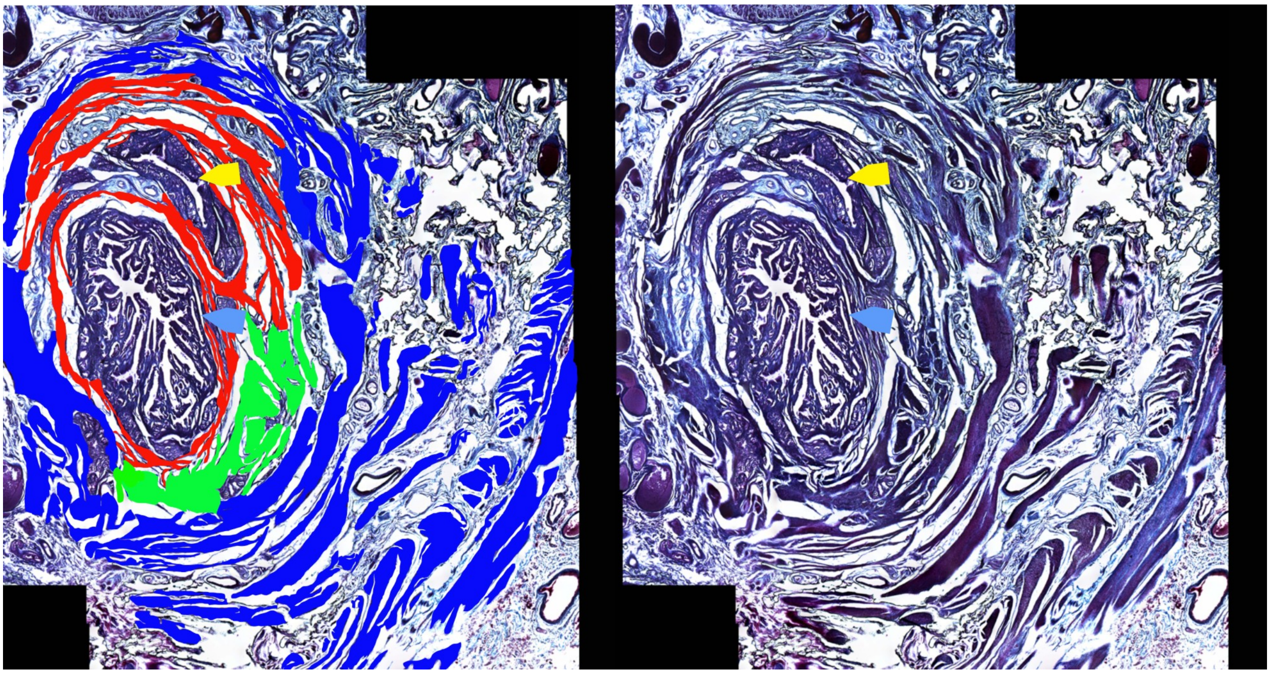


Fig 1. Montage of high-resolution cross-sectional histological sections of the human major duodenal papilla. **A**. Original image showing the relationship between the bile duct (blue arrowhead) and pancreatic duct (yellow arrowhead) to the surrounding musculature. **B**. Muscle fibre classification by location and orientation. Red - circular muscle. Green - longitudinal muscle. Blue - duodenal muscle. Blue arrowhead - bile duct. Yellow arrowhead - pancreatic duct.

subject of several studies (Boyden, 1936; Toouli, 1996; Liashchenko, 1999; Horiguchi and Kamisawa, 2010). Oddi, from whom the sphincter derived its name, was the first to investigate its function in 1887 using manometry (Loukas et al., 2007). Various methods, including histologic sectioning, microscopic dissection and embryologic studies, have been employed in attempts to elucidate the arrangement of the musculature, and thereby help to understand the regulation of biliary secretions (Schwegler, 1937; Ohta et al., 1991; Flati et al., 1994; Toouli, 1996; Liashchenko, 1999; Horiguchi and Kamisawa, 2010; Ando, 2010; Yang et al., 2013). However, the complexity of the interlinking circular and longitudinal muscle fibers as well as their relationship to the musculature of the duodenal wall has limited the ability of these techniques to accurately visualize the sphincter in three dimensions.

Endoscopic sphincterotomy is frequently undertaken when performing endoscopic retrograde cholangiopancreatography (ERCP) to treat biliary and/or pancreatic disorders (Testoni et al., 2016). A better understanding of the musculature of the human PBJ might be of relevance to optimizing technique and reducing morbidities such as duodenal perforation, papillary stenosis and iatrogenic pancreatitis. Similarly, a better understanding of the muscle fiber arrangement in this region may provide further insights into sphincter function and its relationship to the pathophysiology of SOD (Toouli, 1996; Hookman and Barkin, 1998; Kyanam Kabir Baig and Wilcox, 2016).

In recent years, the application of computerized modelling techniques to generate representations of anatomical structures has grown. The use of 3-D reconstructions of computerized tomographic and magnetic resonance scans in clinical medicine has developed in parallel. Structures such as the heart and central nervous system have been imaged using various reconstruction techniques, providing insights into their anatomy and physiology (Tunali et al., 2011; Hopkins et al., 2015). Computerized 3-D reconstruction of serial histologic sections offers a novel approach to visualizing the musculature of the human pancreaticobiliary junction. The aim of this study was to describe the musculature of the human PBJ in detail by generating a 3-D reconstruction from serial histologic sections.

MATERIALS AND METHODS

A single pancreaticoduodenal specimen was removed en bloc from an embalmed cadaver. This was 74-year-old white male, with a BMI of 27. His past medical history was relevant for asthma and hypertension. He had no history of pancreaticoduodenal disease and no past surgical history. The liver and biliary tract were of normal appearance, and periampullary diverticula were not visualized. This cadaver had been bequeathed under a Human Tissue Act (2008).

Histology

Following excision, the specimen, comprising the

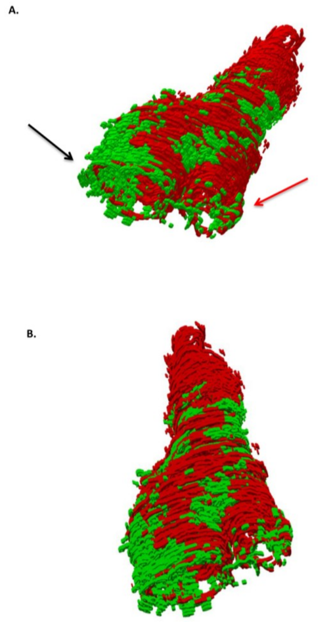


Fig 2. Oblique images of the PBJ (pancreaticobiliary junction) showing the integration of the longitudinal and circular muscle. **A**. Oriented to show the bile (black arrow) and pancreatic (red arrow) ducts entering the PBJ. **B**. Oriented to show the papilla. Colours: Green - longitudinal muscle. Red - circular muscle.

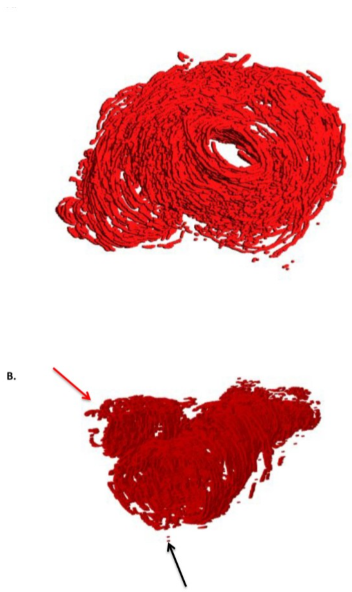


Fig 3. A. Image of the distal portion of the circular muscle of the sphincter within the duodenal wall. **B**. Lateral image showing the discontinuous circular muscle surrounding the proximal portions of the bile (black arrow) and pancreatic (red arrow) ducts.

major duodenal papilla and adjacent duodenum, was trimmed and post-fixed in 10% neutral buffered formalin. The specimen was embedded in paraffin while carefully maintaining its orientation. Next, beginning 100μm from the tip of the major duodenal papilla, 20 μm thick serial axial sections were cut perpendicular to the axis of the lumen. There was an intervening distance of 40 μm between each section. Sections were stained with Masson's trichrome and examined under an Olympus BX51 microscope fitted with a calibrated eyepiece graticule.

Photographs were taken with an Olympus BX61 confocal montaging microscope using a 100x objective lens. A slide montage was constructed by initially creating a well overlay (defining the area over which the sample is scanned), then designating equidistant points on the cross-section of the major duodenal papilla at which images were taken and recorded. The number of images taken was proportional to the size of the histologic section, and was maximal in the centre of the section. The cellular 3D imaging software tool, Volocity 2.0 (PerkinElmer, Coventry, UK) was then used to montage the images (approximately 10 photomicrographs per section), giving a broader cross-sectional view of the major duodenal papilla at specific distances from the tip (Fig. 1).

Image analysis

Images of histologic sections were analysed using Adobe Photoshop 18.1.1 (Adobe Systems Inc., CA, USA). The staining pattern of muscle fibres was used to generate information regarding their location and orientation. Fibres from alternate histologic sections (i.e. at 120 μm intervals) were visually analysed by two observers (NI, SAM) to confirm continuity. Cases of discrepancy were resolved through discussion with a third member of the working group. For each image, the outline of groups of muscle fibres was highlighted based upon their orientation (circular or longitudinal) and location (duodenal or papillary). For the analysis, data points were generated as .exdata files with Matlab R2017a (MathWorks®, MA, USA). Further manual alignment of the data was undertaken using Cmgui 3.0.0 (CMISS, http://www.cmiss.org/). Co-ordinates of the aligned data points were subsequently applied to the raw data with Matlab R2017a software. A 3-D image stack reconstruction was created, using co-ordinate points.

RESULTS

A total of 91 serial cross-sections were reconstructed after combining multiple overlapping photomicrographs at each level.

Circular muscle

Circular muscle was present around the ducts along the entire length of the PBJ specimen (Fig. 2). The circular muscle fibres were particularly dense distal to the confluence of the ducts within

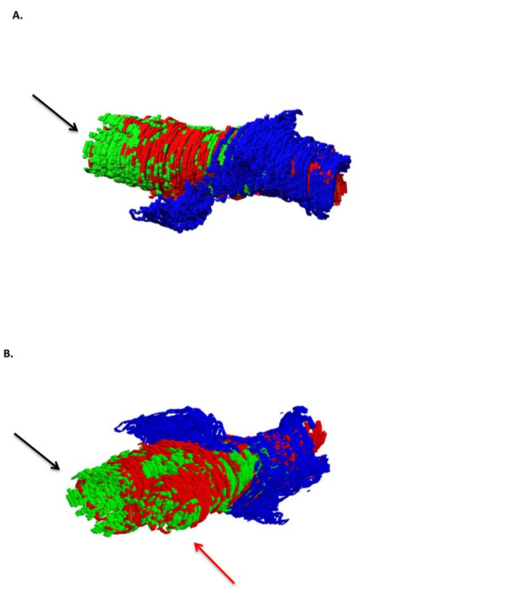


Fig 4. Lateral images of the PBJ (pancreaticobiliary junction) showing the integration of the three muscular structures. **A**. Oriented to show the bile duct (black arrow) entering the PBJ. **B**. Oriented to show the pancreatic duct (red arrow) entering the PBJ. Colours: Green - longitudinal muscle. Red - circular muscle. Blue - duodenal muscle.

the major duodenal papilla. Within this part of the duodenal wall, the muscle fibres appeared progressively more compact (Fig. 3). Despite the presence of surrounding duodenal wall muscle, the circular muscle of the PBJ appeared as a discrete intrinsic structure (Fig. 4). Proximal to their union, the bile and pancreatic ducts were independently encircled by circular smooth muscle fibres.

However, the arrangement of these fibres was irregular and discontinuous. In both histologic cross-sections and 3-D reconstructions, there were no sites where smooth muscle completely encircled each individual duct (Fig. 2B). On the histologic sections, circular fibres were visualized extending into the mucosal folds of the PBJ.

Longitudinal muscle

Longitudinal muscle fibres were seen around the ducts along the length of the PBJ specimen, investing the circular muscle layer (Fig. 2). Proximal to their union, longitudinal muscle fibres were seen in the wall of the terminal bile and pancreatic ducts, being more prominent around the bile duct. Only a few longitudinal muscle fibres surrounded the terminal pancreatic duct (Fig. 5). Distal to the confluence of the two ducts within the duodenal wall, longitudinal muscle fibres were denser but incompletely distributed around the circumference of the sphincter and not extending to the tip of the major duodenal papilla (Fig. 6). The longitudinal muscle fibres were closely related to the muscle of the duodenal wall. Although in some locations indi-

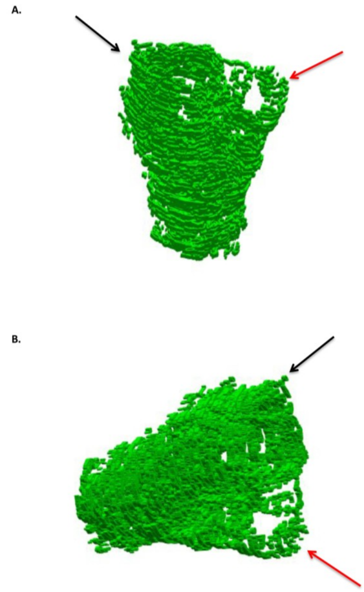


Fig 5. A. Craniocaudal and **B**. Lateral orientation showing the distribution of longitudinal muscle along the pancreaticobiliary junction. Red arrow: pancreatic duct. Black arrow: common bile duct.

vidual circular and longitudinal muscle fibres were discontinuous, together they formed a completely investing muscle layer around both ducts.

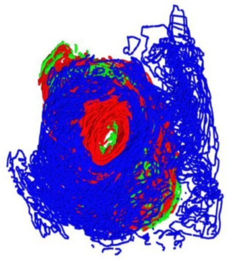
Duodenal muscle

There was a clear distinction between the intrinsic muscles of the PBJ and those of the adjacent duodenal wall, which consisted of an inner circular and outer longitudinal muscle layer external to the PBJ (Figs. 4, 6). The duodenal circular muscle fibres were continuous and more densely arranged near the tip of the papilla (Fig. 6). The outer longitudinal duodenal muscle fibres were not continuous and confined to the superior wall of the PBJ and terminal common bile duct.

DISCUSSION

This is the first study to describe the 3-D anatomy of the muscles of the human PBJ, an important sphincter regulating biliary and pancreatic secretions. We used high-resolution histologic sections of a normal PBJ from a human cadaver to reconstruct the musculature in three dimensions, providing unique images of this junction.

Previous histologic studies have underlined the complexity of the muscle arrangements in this region and representations have been limited to histologic cross-sections or illustrations of gross anatomy dissections (Dardinski, 1935; Hand, 1963; Ohta et al., 1991). Attempts to overcome these limitations using maceration techniques yielded specimens which demonstrated muscle orientations in two dimensions, but the precise arrange-



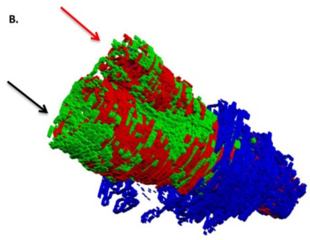


Fig 6. A. Cross sectional image the PBJ (pancreaticobiliary junction) showing the integration of duodenal and circular muscle **B**. Oblique image showing the integration of all three muscle structures. Black arrow: common bile duct. Red arrow: pancreatic duct. Colours: Green - longitudinal muscle. Red - circular muscle. Blue - duodenal muscle.

ment was obscured (Boyden, 1941, 1966).

Studies of foetal specimens have provided insights into the origin of, and relationship between, individual ductal structures at the PBJ, but do not represent the mature structure (Schwegler, 1937; Ohta et al., 1991; Yang et al., 2013). Manometric studies have been used to infer the functional anatomy of the sphincter of ampulla (Habib et al., 1988).

Our study demonstrates the 3-D arrangement of the muscles around the terminal bile and pancreatic ducts, and confirms the sphincter-like arrangement of these muscles, particularly in the duodenal wall and major duodenal papilla distal to the point of ductal union. The sphincter is composed of both longitudinal and circular muscle, with the circular muscle most prominent towards the tip of the papilla. The continuity of the muscle structures suggests that muscle activity around the terminal bile and pancreatic ducts functions in a coordinated manner, and that the combined secretions from both systems are regulated by the sphincter of ampulla surrounding the united ducts.

Further, the existence of muscle fibres extending into the mucosal folds of the PBJ confirms previous histologic observations and supports the notion that the sphincter works in a complex coordinated fashion that includes these mucosal folds (Purvis et al., 2013).

Historically, the muscular function of the PBJ has been the subject of controversy. Oddi first suggested the existence of an intrinsic choledochal sphincter (Loukas et al., 2007) and, although this sphincter may be influenced by the motility and tone of the duodenal wall, it was considered to be structurally and physiologically independent (Habib et al., 1988; Horiguchi and Kamisawa, 2010). An alternative hypothesis proposed that the sphincteric mechanism around the terminal bile duct is enhanced by contraction of the duodenal muscle (Dardinski, 1935; Schwegler, 1937). Our findings suggest that the PBJ has intrinsic muscles that are not intimately interconnected with the duodenal wall musculature and therefore support the former theory. This is supported by embryologic studies demonstrating that the sphincter develops independently of duodenal smooth muscle (Bosch and Pena, 2007; Ando, 2010; Desdicioglu et al., 2012; Yang et al., 2015).

In normal individuals, basal sphincter pressures range between 15 and 18 mmHg and exceed intrabiliary and duodenal pressures (Pfau et al., 2011; Purvis et al., 2013). Effective pressure regulation enables the sphincter to regulate biliary and pancreatic secretions (Toouli, 1984). Prevention of reflux of duodenal contents into the bile duct is considered to be achieved by antegrade peristaltic activity and tonic phasic contractions (Toouli, 1984; Pfau et al., 2011). Our 3-D reconstruction correlates with these functional observations by demonstrating therecomplex arrangement of circular and longitudinal muscle fibres necessary for peristalsis and tonic contraction around the terminal parts of the bile and pancreatic ducts and, most importantly, around the region of ductal union.

Sphincter of Oddi dysfunction is typically diagnosed from a combination of symptoms and manometric findings (Yaghoobi and Romagnuolo, 2015; Kyanam Kabir Baig and Wilcox, 2016). It is a controversial diagnosis that has been attributed to muscular hypertrophy, resulting in sphincter hypertension, and peristaltic dyskinesia. Treatment includes antispasmodic medication and/or ERCP with sphincterotomy (Sandblom and Ivy, 1935; Small and Kozarek, 2015; Kyanam Kabir Baig and Wilcox, 2016). Recent multicentre studies have suggested that endoscopic intervention, which is associated with a significant risk of pancreatitis, does not improve symptoms (Cotton et al., 2014; Kyanam Kabir Baig and Wilcox, 2016).

Our muscle reconstruction images indicate that targeting the distal end of the PBJ would only partially disrupt the muscular sphincter mechanism. Our study has some significant limitations. Firstly, due to the labour-intensive and time-consuming nature of the study, our reconstructed model relates to a single human specimen. The PBJ is known to exhibit variability in the length of the common pancreaticobiliary channel, the angle of entry into the duodenum, the length of the intramural and extramural portions of the ducts, the luminal diameter of the ducts, and the frequency of the existence of separate terminations of the bile and pancreatic ducts (Misra and Dwivedi, 1990; Ishibashi et al., 2000). Therefore, further studies would be required to investigate the variability of the 3-D arrangement of the muscles. Secondly, smooth muscle fibres were categorized as longitudinal or circular but some fibres are probably more oblique in orientation (Cotton et al., 2014).

Thirdly, because inter- and intra-rater variability were not evaluated during fibre classification, we are unable to account for measurement error variance in the 3-D model. Finally, structure can only infer function and caution is needed when considering the physiologic implications of the muscle arrangement.

CONCLUSIONS

To the best of our knowledge, this is the first three-dimensional reconstruction of the muscles of the human PBJ. It provides an insight into the complex arrangement and orientation of the muscular sphincter surrounding the terminal bile and pancreatic ducts and the common pancreaticobiliary channel. Our findings support the well-established concept of an intrinsic muscular sphincter composed of circular and longitudinal muscle fibres that is distinct from the surrounding duodenal muscle.

ACKNOWLEDGEMENTS

We wish to thank Mandy Fisher, Otago Histology Services Unit, University of Otago, Dunedin for her expertise in providing serial histologic sections and those who generously bequested their bodies to the Department of Anatomy at the Otago School of Medical Sciences, Dunedin, New Zealand for anatomical study and research.

Specific author contributions: SAM and MDS conceived and oversaw the project, NP performed the reconstructions, NI and XW facilitated analysis of the reconstructed images, NI wrote the first draft of the article, and SAM and MDS revised the manuscript.

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