REVIEW
ARTICLE

Dynamic Sonographic Tissue Perfusion Measurement

Thomas Scholbach[1], *Jakob Scholbach*[2]*

The amount of blood passing through a tissue is a fundamental parameter since metabolism and its adaptation in disease is reflected by changes of perfusion. To evaluate the functional state of a tissue or an organ it is therefore helpful to know its perfusion intensity. Inflammation for example is highlighted by an increase of perfusion whereas chronic diseases are often accompanied by atrophy of tissue and reduction of organ perfusion. We developed and present here an overview of a simple but sensitive method to quantify tissue perfusion by means of simple color Doppler sonography. This dynamic tissue perfusion measurement (DTPM) uses color hue data to calculate the mean perfusion velocity and color pixel area to calculate the perfused part of a certain region of interest. All data are referred to full heart cycles thus reflecting all changes during a heart beat. With this approach a substantial step forward is made compared to traditional resistance index (RI) or contrast enhanced ultrasound (CEUS) sonographic techniques of blood flow evaluation. This paper describes DTPM basics and shows applications in a variety of fields.

KEY WORDS — tissue perfusion measurement, color Doppler, blood flow

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Conflict of Interest Statements

Both authors have developed the software PixelFlux, used in perfusion measurement. J.S. is the head of the software company Chameleon-Software, distributing the software used in this paper.

Ethics Committee Approval

No ethics committee approval was necessary since all investigations were part of the routine ultrasound investigations for which a written informed consent was given by the patients or their parents.

Introduction

Measurement of perfusion is of outstanding interest in monitoring many disorders. A non-invasive, non-ionizing, reliable and affordable tool is needed to base clinical decisions on quantitative perfusion data. The novel software-based (PixelFlux) dynamic technique of color Doppler signal quantification from sonographic video meets these needs. This method has opened up new perspectives in oncology [1], nephrology [2–4], gastroenterology [5] and transplantation medicine [2,4] and even spurred new disease concepts based on a quantitative pathophysiologic evaluation of organ perfusion [6].

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Quantitative knowledge of perfusion could directly influence clinical decisions in disorders characterized by relevant perfusion changes such as inflammation, tumor growth and necrosis, transplant rejection, organ failure and arterial stenosis. After the first attempts to quantify tissue perfusion by counting color Doppler signals in still images [7–10] several reports on the use of quantitative Doppler signal analysis with and without contrast enhancing agents have been published so far [11–15]. Despite such developments it is not easy to get reliable tissue perfusion data in a reliable, non-invasive, non-ionizing, cheap and patient-friendly manner. Sonographic procedures have many advantages over other techniques: computed tomography (CT) (radiation exposure, no flow quantification), magnetic resonance imaging (MRI) (costs, spatial resolution, availability, discomfort to patients), scintigraphy (no morphologic information, radiation), and positron emission tomography (PET) (costs, availability, no morphologic information). Unfortunately existing sonographic perfusion evaluation techniques are misleading [resistance index (RI)], invasive and expensive (contrast enhancers) or imprecise (vessel counting in still images). Therefore we propose a novel software-based Dynamic Tissue Perfusion measurement technique (DTP) [16] capable of extracting dynamic (changing with heart action) flow data of the perfused area and instantaneous perfusion velocity in an arbitrarily chosen region of interest from a standardized sonographic video, which also needs no contrast enhancer injection.

Principle of Dynamic Sonographic Tissue Perfusion Measurement

Idea

The guiding idea behind the dynamic DTP is to quantify tissue perfusion by referring to all relevant parameters which influence the total amount of blood passing through a tissue section during a complete heart cycle. These are the mean perfusion velocity of all vessels and the mean perfused area of the tissue section under investigation. Both are directly proportional to the amount of transported blood. Both do also change significantly during one complete heartbeat. It is therefore necessary to start with the measurement of these two basic parameters at the beginning of a heartbeat and to continue in as short time intervals as possible to the end of the heart beat. This is important because great differences between momentary systolic and diastolic perfusion even in tiny vessels may exist (Fig. 1). From these data a mean perfusion velocity, as well as a mean perfused area is calculated, thus referring all measurements to the very basic rhythm of perfusion—one complete heart cycle. By multiplication of these mean values—mean perfused area and mean perfusion velocity—the mean perfusion intensity is calculated. The mean perfusion intensity is thus also referred to as the area of the tissue section which is captured by the region of interest (ROI) of the current investigation: mean velocity (v) of all pixels is multiplied by the area (A) of all colored pixels and divided by the area of the ROI. Thereby the mean flow intensity value of the ROI (I) is calculated.

$$I\ [cm/s] = A\ [cm^2] * v\ [cm/s] / A_{ROI}\ [cm^2]$$

Following this algorithm, a true dynamic (with respect to the ever changing values during a full heart cycle) mean perfusion intensity can be calculated for a tissue section in a freehand or geometrically standardized ROI. As with any measurement a crucial point is standardization—in DTPM it is the presetting of the ultrasound equipment. The color Doppler frequency as well as the gain have to be kept constant for comparable investigations. Color flow velocity settings may be changed to avoid aliasing if necessary. The software recognizes the change of color scale values automatically.

New kinds of numerical perfusion information

Dynamic tissue perfusion measurement goes far beyond existing techniques with respect to numerical description of perfusion in tissues. In addition to

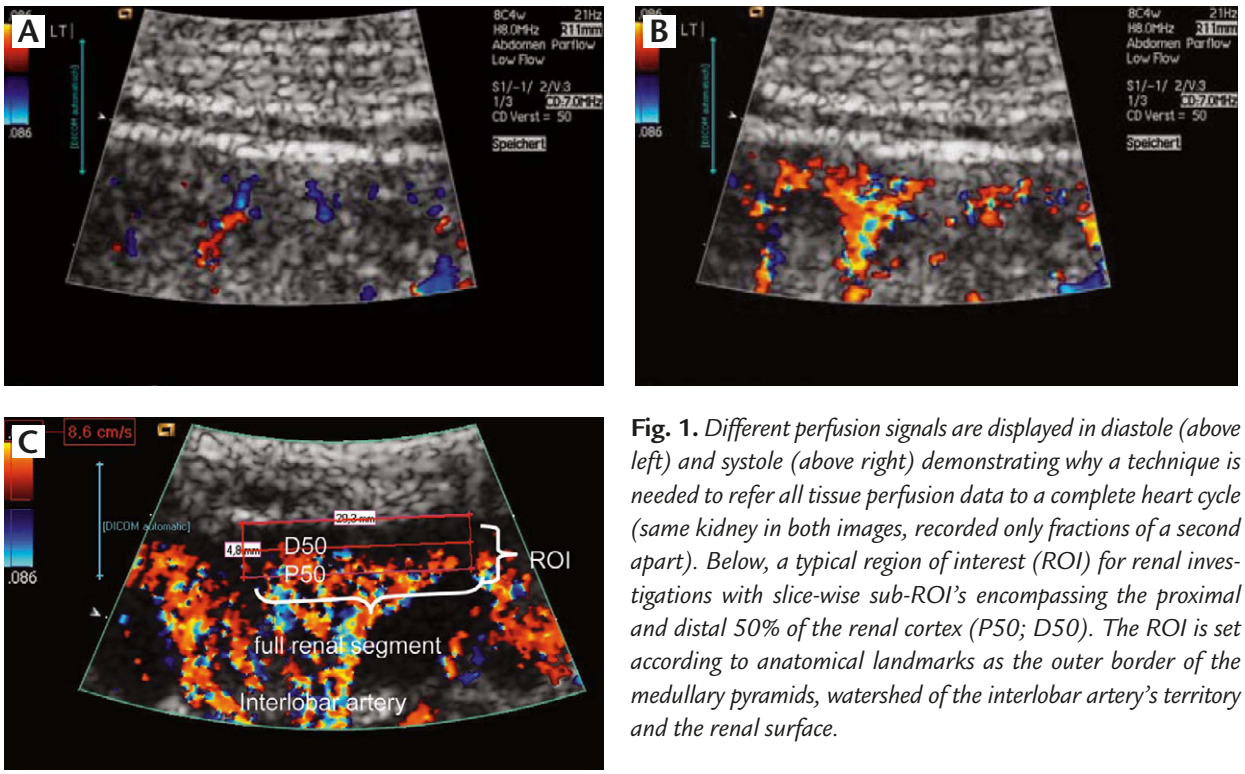


Fig. 1. *Different perfusion signals are displayed in diastole (above left) and systole (above right) demonstrating why a technique is needed to refer all tissue perfusion data to a complete heart cycle (same kidney in both images, recorded only fractions of a second apart). Below, a typical region of interest (ROI) for renal investigations with slice-wise sub-ROI's encompassing the proximal and distal 50% of the renal cortex (P50; D50). The ROI is set according to anatomical landmarks as the outer border of the medullary pyramids, watershed of the interlobar artery's territory and the renal surface.*

Parameter unit	V_{mix} cm/s	V_{red} cm/s	V_{blue} cm/s	A_{mix} cm^2	A_{red} cm^2	A_{blue} cm^2	I_{mix} cm/s	I_{red} cm/s	I_{blue} cm/s
Average	3.715	3.526	3.903	0.043	0.025	0.061	1.286	0.858	1.715
TRI	0.777	1	0.555	0887	1	0.775	0.868	1	0.735
TPI	1.179	1.53	0.828	2.353	3.527	1.179	2.709	4.154	1.264

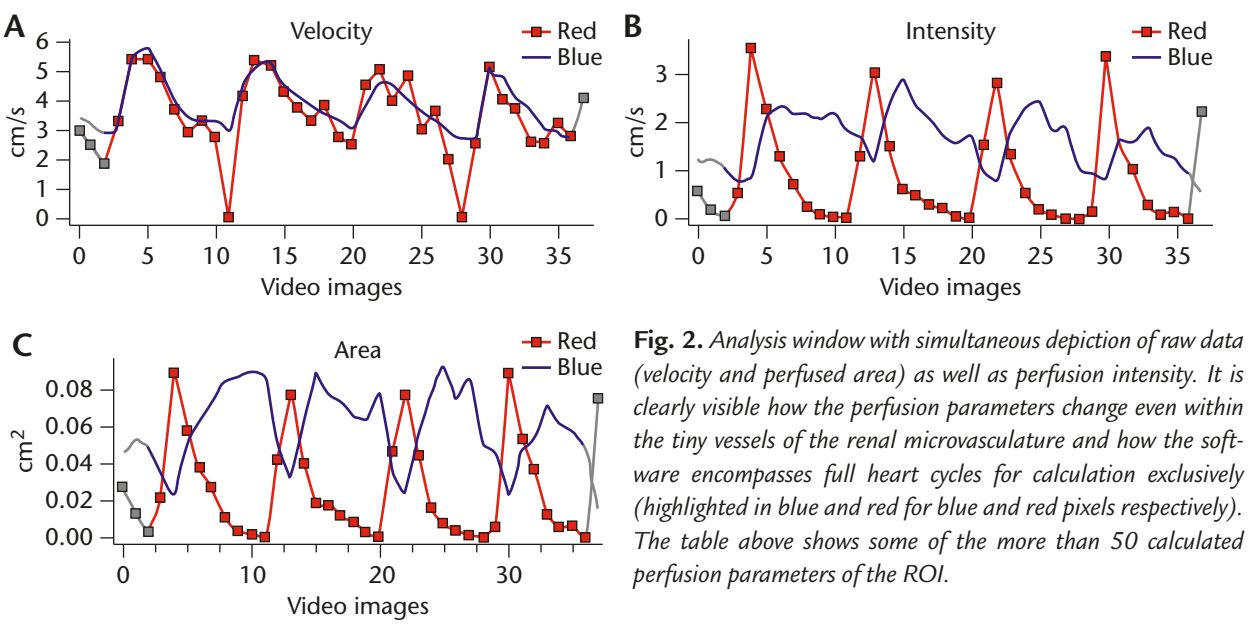


Fig. 2. *Analysis window with simultaneous depiction of raw data (velocity and perfused area) as well as perfusion intensity. It is clearly visible how the perfusion parameters change even within the tiny vessels of the renal microvasculature and how the software encompasses full heart cycles for calculation exclusively (highlighted in blue and red for blue and red pixels respectively). The table above shows some of the more than 50 calculated perfusion parameters of the ROI.*

mean perfusion intensity calculations, new parameters are generated to describe the dynamics of perfusion. Examples are the Tissue Resistance Index (TRI) and the Tissue Pulsatility Index (TPI). TRI and TPI may refer to velocity, intensity and perfused area according to the following formulas:

$$\mathrm{TRI}(x) = (\text{maximum of } x - \text{minimum of } x)/\text{maximum of } x$$

- Where x represents velocity or intensity or perfused area
- x is the mean value of x for the entire ROI during a full heart cycle

$$\mathrm{TPI}(x) = (\text{maximum of } x - \text{minimum of } x)/\text{mean of } x$$

- Where x represents velocity or intensity or perfused area
- x is the mean value of x for the entire ROI during a full heart cycle

A dynamic perfusion map is generated to pinpoint the local perfusion in a sub-millimeter graded fashion numerically with false colors (see Figs. 10 and 11). Moreover the distribution of perfusion intensities according to the whole spectrum of occurring intensites, which are assigned to one of 33 intensity classes, is calculated and diagrammatically displayed. Thus tissues may be compared according to their content of stronger or weaker perfused areas and vessels (see Figs. 3 and 4).

The perfusion intensity of a ROI as a whole is displayed as a false color map covering the whole ROI. High local perfusion intensities are displayed in red, medium ones in white and lower ones from grey to black. To describe these intensities more precisely a diagram shows the relative frequency of the occurring local intensities. To achieve this, all occurring intensities are assigned to 33 classes forming the x-axis and encompassing the complete intensity spectrum from 0 to maximum in equal proportions. Each single class contains thus a certain amount of pixels fitting to the respective intensity class. This amount is outlined at the y-axis as frequency of occurance in percent of the total number of colored pixels. This way a distribution curve of all 33 intensity classes is constructed which at one glance displays the characteristic intensity distribution curve of the respective ROI. In addition, these curves can be described mathematically in more detail. Distribution curves may be bell shaped or Gaussian or may divert from this well known pattern. They may be skewed to the left or right thus resembling the slope of a hill with one steep side and one flat side. And the curves may exhibit a more peaked or a more planar shape. These different shapes are numerically described as skewness and kurtosis. Both are general parameters of any distribution. Their numerical description offers new approaches to pinpoint subtle shifts of the vascular microarchitecture.

Altogether more than 50 perfusion parameters are calculated to describe the tissue perfusion numerically.

Advantages Over Existing Methods of Sonographic Perfusion Evaluation

A comparison of dynamic tissue perfusion measurement to conventional resistance index measurements and contrast enhanced sonography (CEUS) is given (Table).

Practical Issues of Dynamic Tissue Perfusion Measurement

Perfusion measurements were carried out automatically with dedicated software (Pixelflux, Chameleon-Software, Leipzig, Germany). Color Doppler sonographic investigations of kidneys and renal transplants were performed with a 4–8 MHz curved array probe and a 5–8 MHz linear array transducer in intestinal and other investigations was applied using "Sequoia 512" ultrasound equipment (Acuson/Siemens, Mountainview, California). Videos of 3 seconds duration of kidneys, renal transplants, bowel segments, tumors and lymph nodes were recorded.

Table. Advantages of dynamic tissue perfusion measurement

Dynamic tissue perfusion measurement	Resistance index measurement	Contrast enhanced sonography
Measurement of perfusion in all vessels of a large ROI	Single point measurement	Measurement of contrast enhancement in a large ROI
Measurement of flow velocities of all pixels in all vessels' transsection	Measurement of flow velocities only in some pixels of a vessel (sample volume)	No flow velocity measurement
Appreciation of heart beat specific flow dynamics	Appreciation of heart beat specific flow dynamics	Loss of heart beat dynamics—saturation curves are calculated
All relevant raw data (i.e. velocities and areas of perfusion) are measured directly during complete heart cycles	Only systolic and enddiastolic velocities are measured	Perfusion intensity is evaluated indirectly from contrast enhancer influx curves (steepness of influx and level of saturation)
Use of unmodified raw data	Use of unmodified raw data	Contrast enhancer as additional source of error
Realistic overall tissue perfusion measurement	Overestimation of flow due to compensatory hyperperfusion of surviving vessels in a tissue with shrinking overall perfusion	Overall tissue perfusion measurement derived from secondary data (influx characteristics)
Noninvasive	Noninvasive	Invasive
Unrestricted observation time	Unrestricted observation time	Decay of contrast enhancer limits observation time
No side-effects	No side-effects	Potentially hazardous side-effects
Cheap	Cheap	Expensive contrast enhancer
Fast	The fastest	Time consuming

In kidneys the ROI was chosen in the renal parenchyma in the area between the outer border of medullary pyramids and the kidney surface (Figs. 1 and 3) [1–3]. A parallelogram is placed to enclose a complete vascular segment which is fed by the interlobar artery running straight towards the transducer. This way a symmetric distribution pattern of all branches of this vascular segment is achieved. This parallelogram is divided into two segments (p50, d50) encompassing the proximal 50% (p50) or distal 50% (d50) of the ROI's height [1–3].

In other organs and tumors a freehand ROI is useful. In some cases sub-ROIs may be defined by concentric circles with pre-defined relational diameters.

Examples of Application

To demonstrate the broad applicability of the dynamic tissue perfusion measurement technique, some examples of clinical applications are given below.

Renal transplants

The survival of renal transplants depends basically on a sufficient perfusion of the entire cortex. Histologic

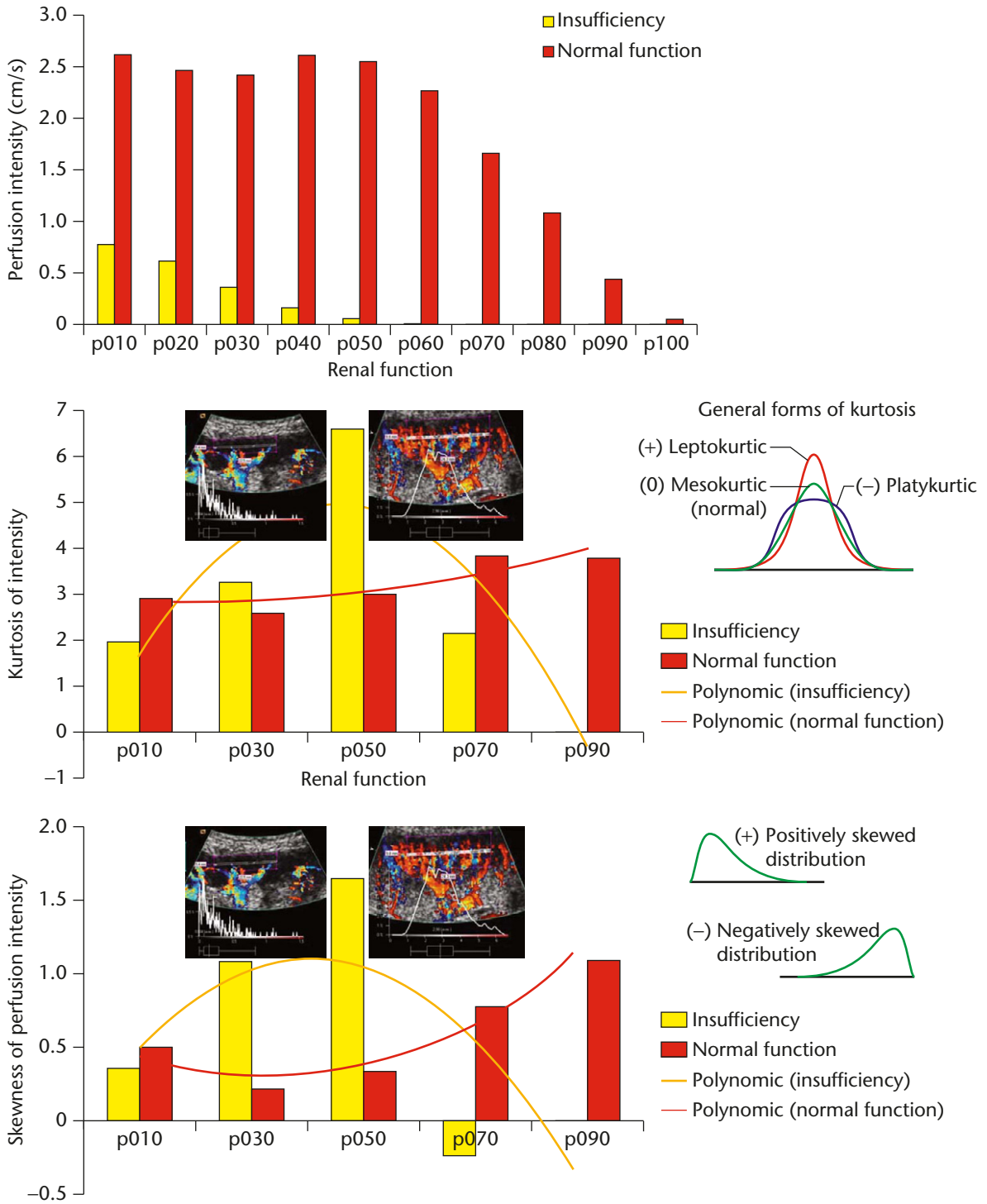


Fig. 3. *Comparison of slicewise perfusion intensities of both kidneys in Figure 4. P010 to P100 are 10% slices of the cortex from center to periphery. Both kidneys are clearly discriminated by a striking loss of perfusion inside the insufficient kidney. This is in overt discrepancy to equal resistence indices (RI) of 0.66 in the interlobar arteries of both kidneys. Comparison of skewness and kurtosis in five cortical slices each encompass 10% of the cortex from the center (p10) to the periphery (p90). Overt differences of both parameters and their change within the cortical vascular tree are visible in two kidneys with different function but equal RI of 0.66. Kurtosis and skewness peak in the central cortex of the insufficient kidney but tend to rise from the center to the periphery in the normal kidney. Insets show actual distribution curves in slice p050 illustrating the differences of both perfusion intensity distributions in both kidneys (left insufficient, right inset normal function). Colored lines are tends of the corresponding columns.*

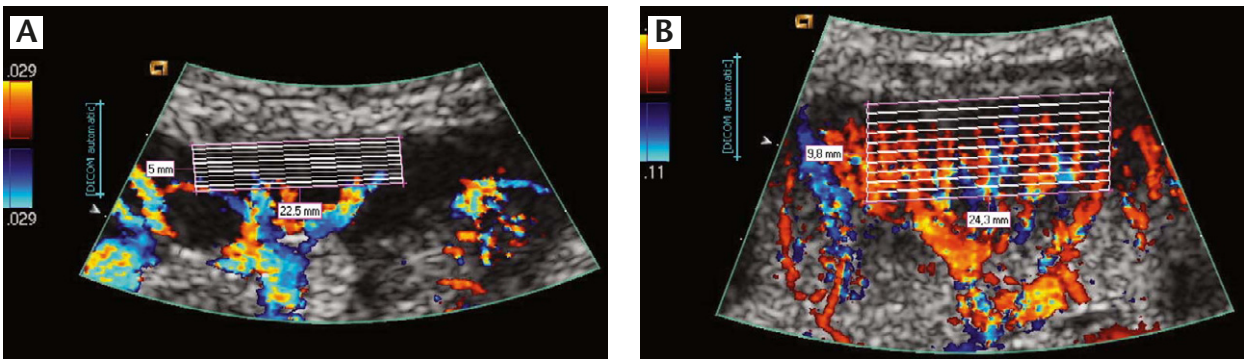


Fig. 4. *Color Doppler sonographic images of two renal transplants. The left image is from an insufficient organ (creatinine 231 µmol/L) whereas the right stems from a healthy organ (creatinine 70 µmol/L). Despite the fact that the left image is depicted with low flow color scale compared to the right image it is clearly seen that the subcapsular vessels are diminished and only the stem vessels of the cortical segment are still perfused. The cortex is divided horizontally into 10 equal slices to measure and compare their perfusion, kurtosis and skewness.*

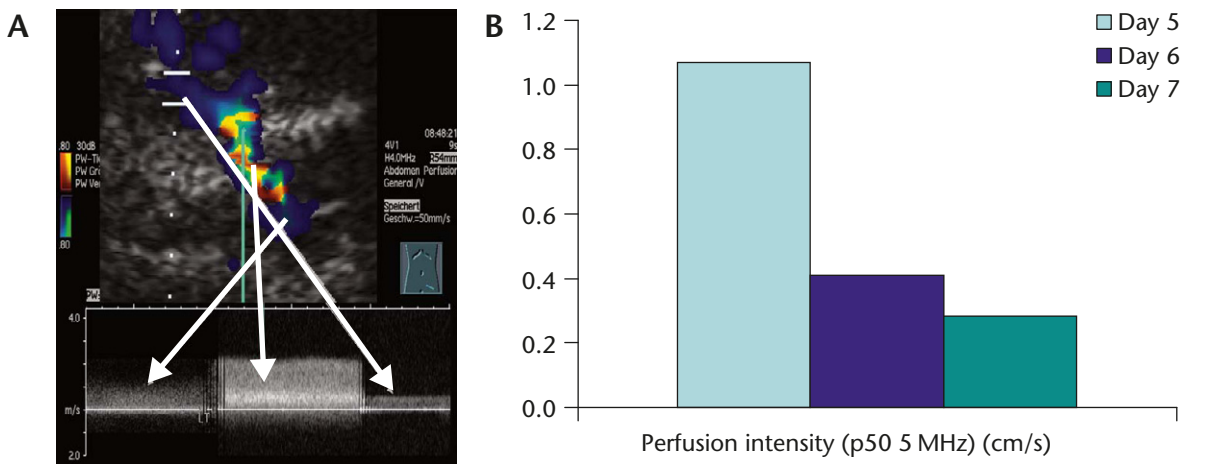


Fig. 5. *Evalution of a progressive but still incomplete acute thrombosis of a renal transplant's vein. Perfusion intensity measurement of the cortex shows clearly the impact of venous congestion on cortical perfusion.*

damage may occur very early as a consequence of medication or chronic rejection.

A numerical, non-invasive description of the transplant's microvasculature is therefore of crucial interest as a follow-up parameter [2–4].

To illustrate the advantage of a tissue perfusion measurement over the conventional evaluation of the kidney with the RI consider the examples in Figs. 3–5 (same patients).

RI measurements in three interlobar arteries of both transplants revealed identical values of 0.66. Not only are these RI identical despite clearly different perfusion and function of both transplants, the RI of 0.66 is also quite normal even in the malfunctioning transplant. This measurement is in striking contrast to the bad coloration of the insufficient kidney (Fig. 4A) compared to the healthy one. Only dynamic tissue perfusion measurement can reflect these perfusion changes adequately (Figs. 4 and 5). The impact of venous obstruction onto transplant perfusion can also be shown by DTPM (Fig. 5A) offering a decision aid in incomplete thromboses.

In a series of 38 renal transplants we could demonstrate a swift and significant decline of cortical perfusion which was especially pronounced in the distal 50% region (D50) [2]. In parallel we could show that the novel parameter of tissue perfusion pulsatility was rising significantly in these transplants [4].

Renal Insufficiency

Renal insufficiency develops often unnoticed. Compensatory functional capacity of the kidneys prevents the rise of serum creatinine until substantial and irreversible loss of glomeruli has occurred. Detection of the early stages of renal function loss and description of the compensatory processes is therefore of major concern to nephrologists. Early signs of microvessel loss might serve as a signal to counteract the damaging process as long as it still can be stopped or reversed.

In a developing renal insufficiency (Fig. 6) a preceding loss of proximal microvasculature is seen (P50) whereas a compensatory hyperperfusion in the distal cortex (D50) thwarts the rise of creatinine (unpublished results from 119 patients with normal function and varying degrees of renal insufficiency).

Diabetes Mellitus

Nephropathy is a frequent serious complication of longstanding diabetes mellitus and an increasing burden for patients and health care providers. Today, diagnosis of diabetic nephropathy is made by detection of albumin in urine. First examples from diabetic patients without proven nephropathy have shown this to be a possibly late sign. Fig. 7 shows obvious differences of proximal cortical perfusion patterns in a kidney of a diabetic patient without overt signs of a diabetic nephropathy. The perfusion intensities are shifted towards lower values (peak of the distribution curve left from the mean value) whereas in a healthy kidney perfusion intensities range mostly right from the mean value in this cortical stratum. Intensity distribution curves are a potentially most valuable tool offered by the new DTP technique. Perfusion pecularities of a tissue thus become visible at a first glance. Progression of microvessel damage leads to a shift from one vessel subpopulation to another. This is mirrored by a change of the intensity distribution curve as shown in this example of an otherwise "healthy" kidney of a diabetic individual. Such functional shifts of intracortical perfusion distribution might be a very early sign of impending manifest tissue damage. Their detection with DTP intensity distribution curves would offer therefore outstanding opportunities to prevent manifest disease or to alleviate its course.

Renal Artery Stenosis

In patients with renal artery stenosis it is sometimes difficult to monitor the stenosis sonographically at its very site because of obesity and bowel gas obstructing the view at the entire length of the renal artery. DTP provides welcome information to learn more about the functional sequelae of the diminished perfusion of the cortex, where the crucial renin secreting juxtaglomerular apparatuses are situated.

In addition to the loss of cortical perfusion intensity the slice-wise examination of the renal arterial tree in reproducible, millimeter thin layers gives numerical data on the affection of the larger, smaller and tiniest cortical vessels since their respective proportion differs by the distance of the measurement level to the arcuate artery level. DTPM in standardized cortical levels thus describes regressive functional and morphological changes of the affected kidney at once.

From the still images in Figure 8 a malperfusion of the left kidney can only be assumed. Less coloration of the sonogram could be a hint to diminished overall perfusion. Nevertheless this effect could also be produced by recording of both images at different points of the heart cycle—in diastole much less coloration is found than in systole (see Fig. 1). With conventional means no conclusion can be drawn from such images. DTP takes into account each single image of the entire heart cycle and evaluates all pixels with respect to both flow velocity and perfused area. This way a very subtle measurement of the effective cortical tissue perfusion becomes feasible which yields striking differences between both kidneys as demonstrated in the diagram (Fig. 8). The effect of therapy can also be measured directly at the site where it is functionally important—in the renal cortex. Independently

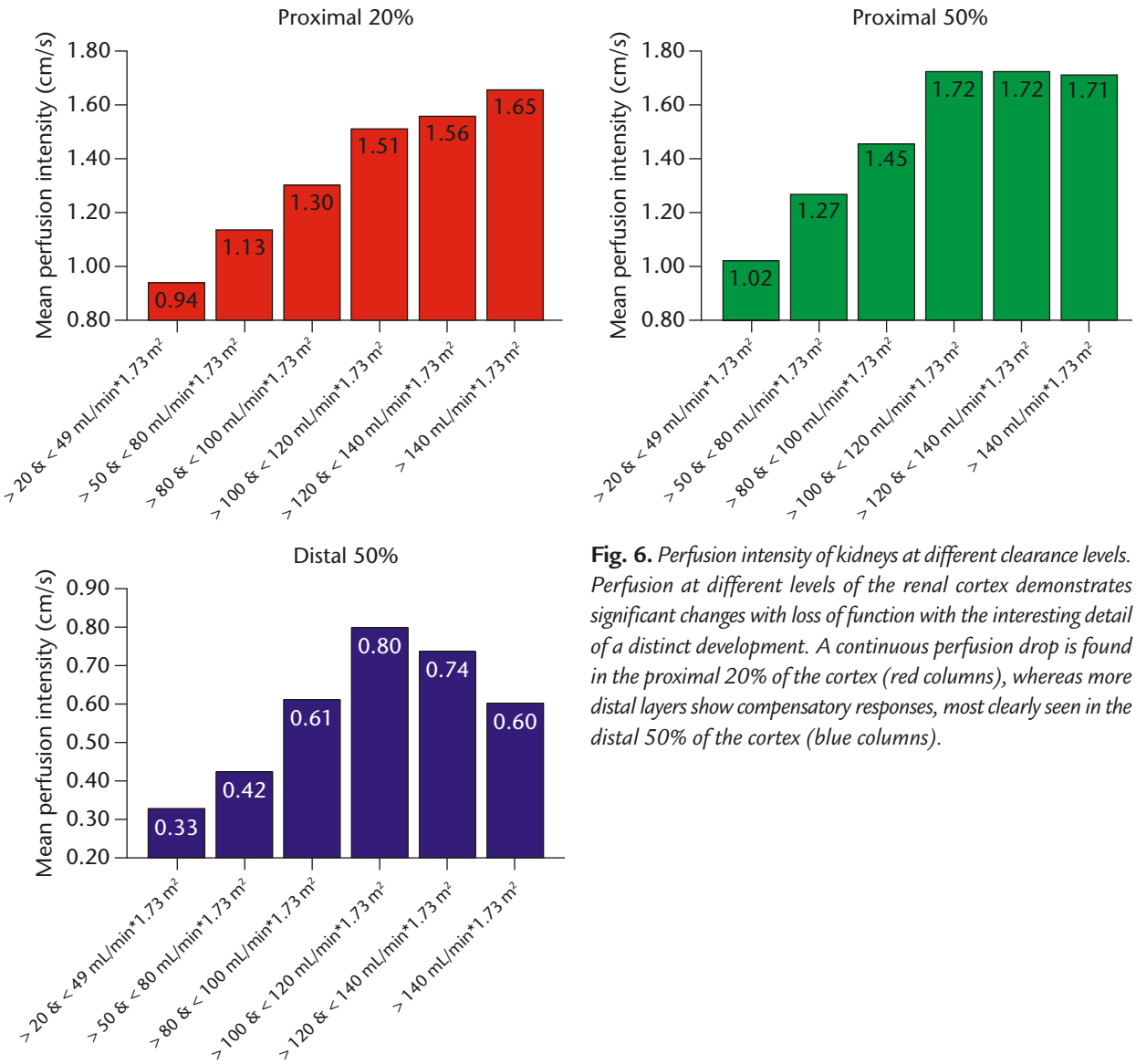


Fig. 6. *Perfusion intensity of kidneys at different clearance levels. Perfusion at different levels of the renal cortex demonstrates significant changes with loss of function with the interesting detail of a distinct development. A continuous perfusion drop is found in the proximal 20% of the cortex (red columns), whereas more distal layers show compensatory responses, most clearly seen in the distal 50% of the cortex (blue columns).*

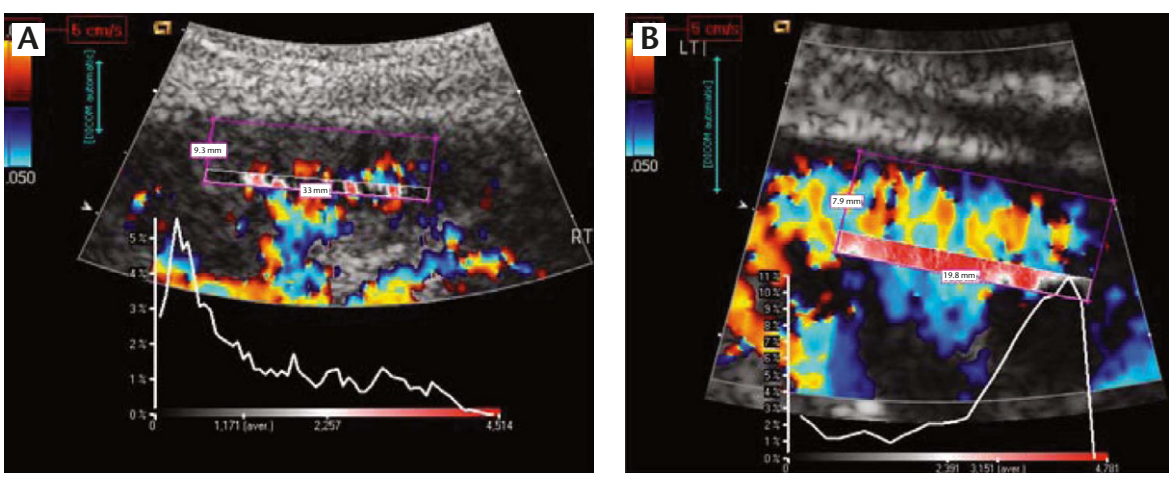
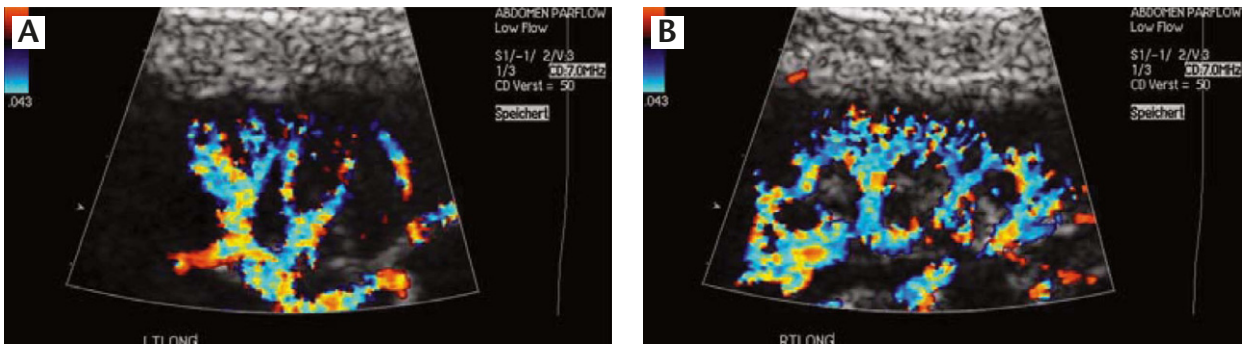


Fig. 7. *Strikingly different perfusion patterns in a kidney of a diabetic patient without overt signs of diabetic nephropathy (A) compared to a healthy kidney (B), perfusion relief of the proximal 20% of the renal cortex.*



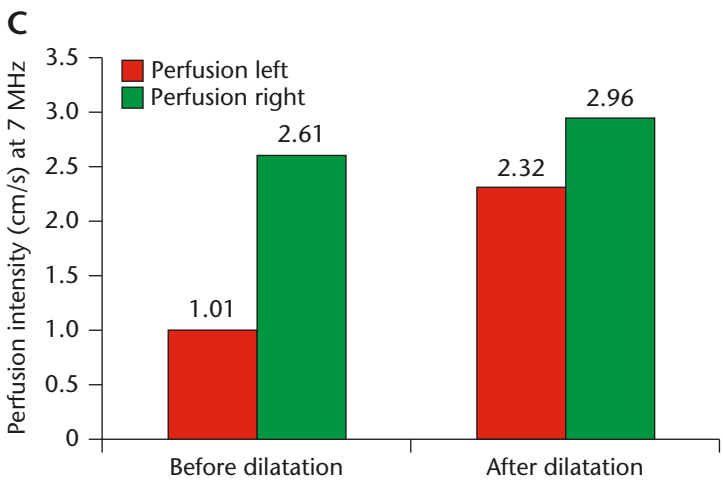


Fig. 8. *(A, B) Left and right sonograms demonstrate the parenchymal Doppler display of the cortical perfusion of the left kidney and right kidney respectively. (C) The diagram shows perfusion intensities of the left (red column) and right kidneys (green column) before and after dilatation.*

from a remaining residual pressure drop at the site of the dilated stenosis a profound amelioration of tissue perfusion can be clearly demonstrated in this patient (compare red and yellow columns in Fig. 8). Perfusion of the left kidney has risen from 1.01 to 2.32 cm/s and increased thus from 44 to 88% in the right kidney which had a perfusion of 2.61 and 2.96 cm/s respectively. The DTP technique offers thus relevant data from exactly where the renal function is exerted which cannot be obtained by any other existing method in such a patient-friendly, convenient and economic manner.

Chronic Inflammatory Bowel Diseases (IBD)

Diagnosis in patients with IBD is often delayed due to the lack of pathognomonic clinical signs, the creeping onset of the disease and unreliable and unspecific laboratory data. To overcome this, disease activity indices which are calculated from a mixture of anamnestic, clinical and laboratory data are in use. The sheer multitude of the recommended indices indicates the basic problem of their application. Invasive diagnostic methods such as enteroscopy, barium enemas and radiologic techniques are applied only late on in many cases because they are inconvenient, ionizing, expensive or painful. A high degree of suspicion has to be reached to convince patients to agree with these measures. The invasiveness of some procedures raises the threshold for applying them. Their late use postpones accurate and early diagnoses.

Classical sonography offers an alternative but is limited despite the fact that morphologic changes of the bowel wall can be demonstrated readily. Nevertheless, the estimation of disease activity by

simple observation of perfusion with color Doppler can at best give a subjective impression of the inflammatory hyperperfusion (Fig. 9). Perfusion intensity measurement in a freely selected part of the bowel wall can thus combine the patient-friendliness of sonography with the exact description of disease activity as currently only known from histological specimens. Our own unpublished comparisons of local histological investigations in bowel biopsies from patients with IBD demonstrated significant correlation of criteria such as neutrophil mural invasion, reduction of goblet cell counts, density of crypt abscesses, lymphocytic infiltration of the bowel wall and intestinal wall edema.

Tumors

In oncology a meticulous description of tumor perfusion is important to measure the effect of therapy, to evaluate the tissue oxygenation being a determinator of responsiveness to chemo- and radiotherapy, and to describe the development of the tumor. DTP clearly has the potential to meet these demands (Fig. 12). Before therapy, perfusion intensity of the metastasis is lower than that of surrounding tissue. Due to chemotherapy a total breakdown of metastasis perfusion occurs whereas healthy liver tissue is hit less severely—as shown by a moderate decline of its perfusion intensity. This is an illustration of the specificity of the therapeutic modality applied on the one hand and a proof of its efficacy on the other. We demonstrated a significant correlation of invasively measured tumor oxygenation with PixelFlux perfusion measurements and could also show, that tissue pulsatility of tumors differ significantly among different N-classes [16].

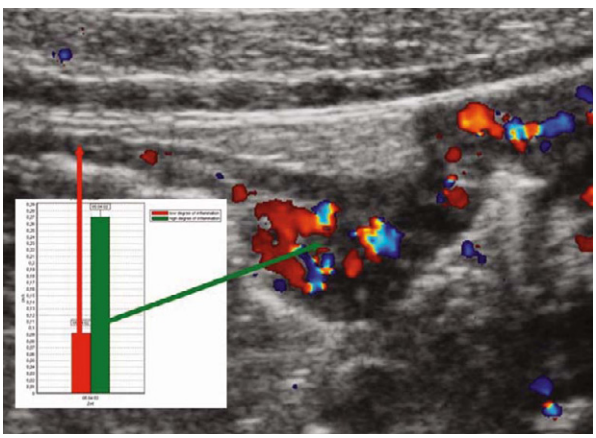


Fig. 9. *The transition from normal to affected transverse colon in a patient with Crohn's disease is shown along with the measurement of the perfusion intensity at both sites.*

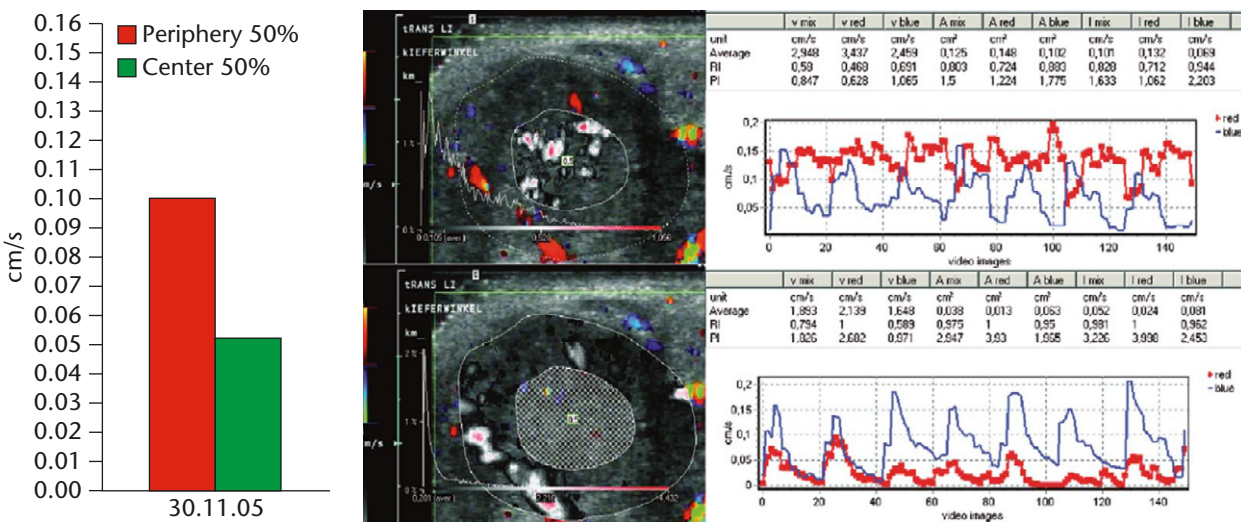


Fig. 10. *Evaluation of tumor perfusion with the target-like region of interest (center). In predefined rings around a core region (here 50% of the tumor's diameter was chosen as core and the peripheral 50% as the surrounding tumor periphery) a standardized measurement of perfusion is carried out. Central and peripheral tumor perfusion can be compared directly (diagram at the left—periphery (red) and center (green)) and characteristics of pulsation of tumor perfusion may also be evaluated (right diagram).*

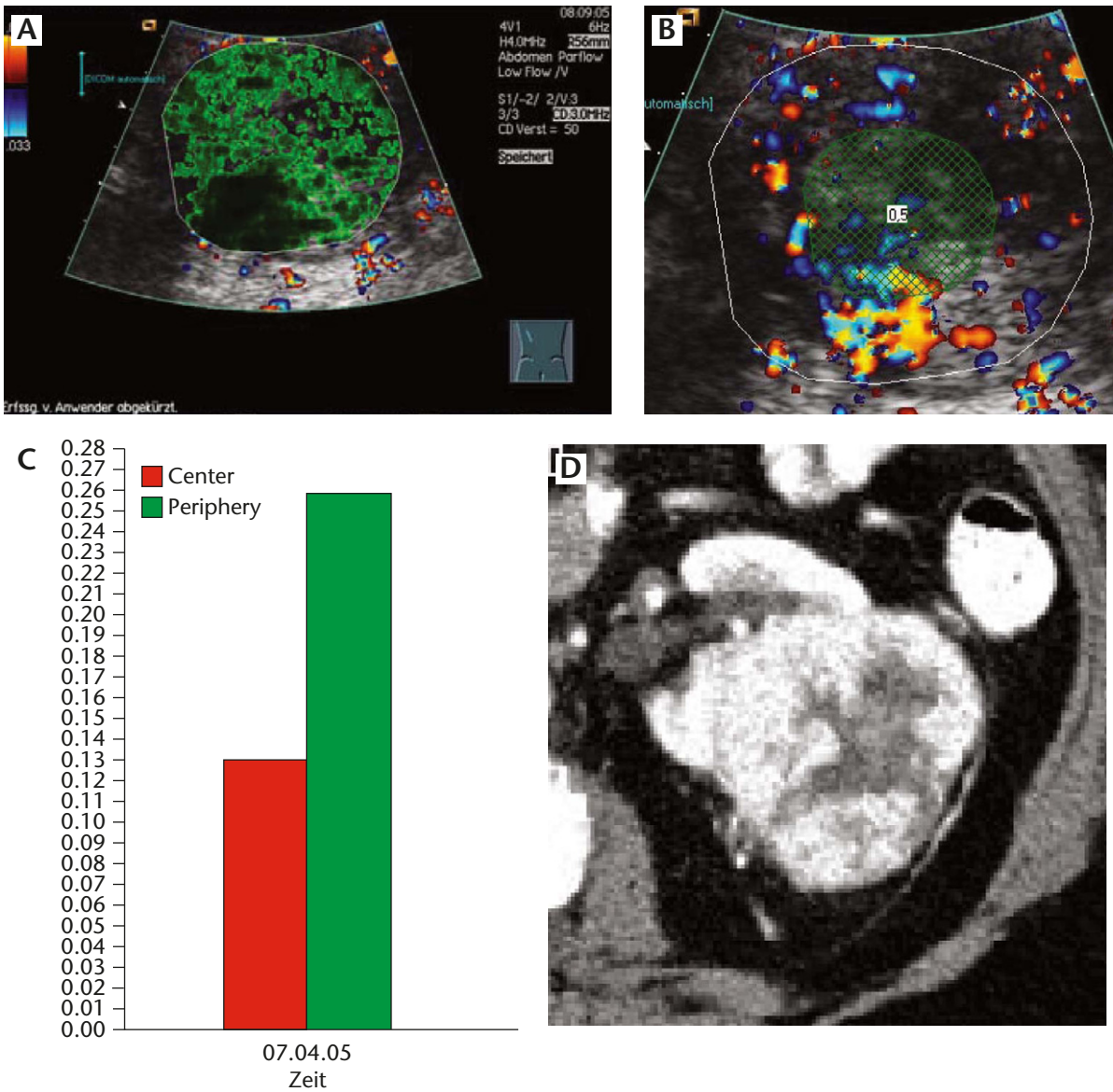


Fig. 11. *Renal carcinoma. (A) Map of pulsatility of perfusion of a tumor transsectional image. (B) Concentric region of interest for simultaneous measurement of perfusion in the tumor center and periphery (selected center in this image encompassing 50% of tumor's diameter). (C) Diagram showing tumor center (red column) and periphery (green column) perfusion intensity (cm/s average of entire ROI). (D) CT of same tumor demonstrating centrally decreased uptake of contrast medium (histology: renal cell carcinoma with strong vascularization and local hemorrhages, central regression with scarring).*

Clearly further studies are necessary to determine the significance of the dynamic perfusion measurement among existing techniques [17].

Fetuses

Fetal well being depends basically on a sufficient perfusion of the fetus as a whole and of each organ respectively. Nowadays the standard of fetal perfusion evaluation is the RI measurement in the umbilical artery as well as in the middle cerebral artery. The comparison of both leads to the diagnosis of so-called brain sparing as a sign of fetal compromise. With the PixelFlux technique it is now possible to quantify the whole fetal perfusion by a spatially angle-corrected perfusion measurement inside the umbilical vein (Fig. 13). The step

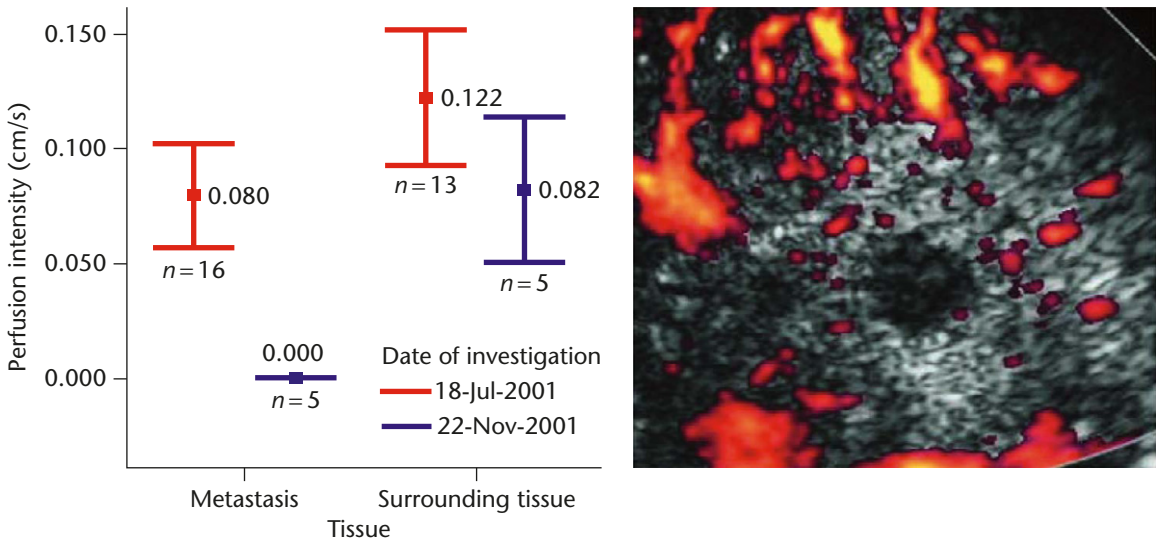


Fig. 12. *Measurement of a therapy effect onto a liver metastasis and its healthy liver environment.*

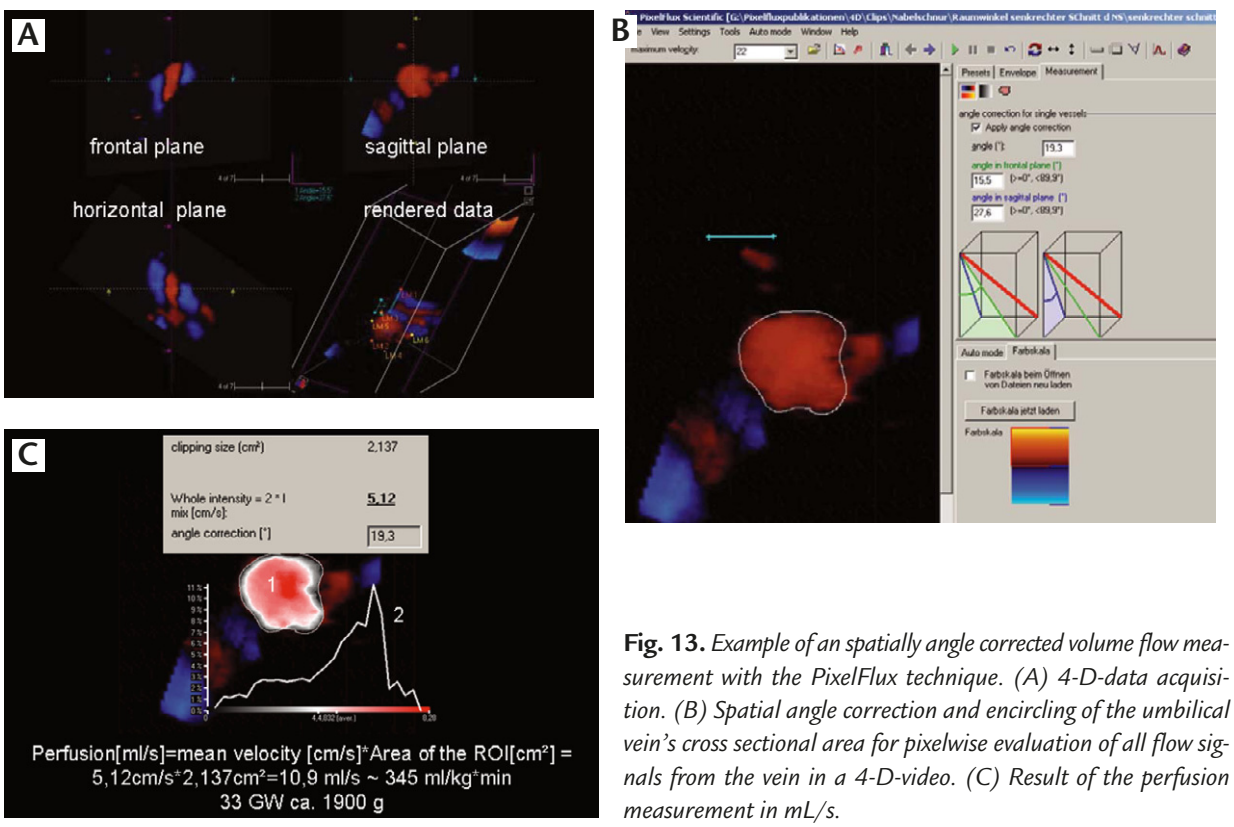


Fig. 13. *Example of an spatially angle corrected volume flow measurement with the PixelFlux technique. (A) 4-D-data acquisition. (B) Spatial angle correction and encircling of the umbilical vein's cross sectional area for pixelwise evaluation of all flow signals from the vein in a 4-D-video. (C) Result of the perfusion measurement in mL/s.*

beyond conventional flow velocity measurements with the PW-Doppler technique has become possible by the pixelwise flow velocity evaluation of the full venous cross sectional area after four dimensional (space and time) recording of the umbilical cord. Thus a calculation in mL/s of the entire fetal perfusion becomes feasible.

Another application is placenta perfusion measurement where first results indicate that perfusion changes invisible to the naked eye of the obstetrician

can be quantified [18]. The perfusion of the maternal side of the placenta can be compared to the fetal one (paper submitted for publication). This could have a major impact on monitoring of pregnancies and could eventually guide therapeutic procedures. Future applications are fetal renal and cerebral tissue perfusion quantification, to describe the organ specific reactions to circulatory compromise and hypoxia during pregnancy in a more detailed manner.

Discussion

Perfusion measurement of an organ or structure without doing harm to the patient, without applying visualization enhancers (contrast media), avoiding the risk of side effects, without radiation, at low cost and with wide availability, are important demands to improve healthcare for many patients. A great diversity of diseases could be evaluated more precisely and a greater number of patients could be diagnosed and treated more reliably with such a method at hand for the practitioner and the hospital physician: inflammatory, vascular (arterial, venous or microvascular), neoplastic, degenerative diseases—all are accompanied by relevant changes of perfusion in the affected tissues. To measure these changes reliably would certainly allow monitoring these disorders more closely than today, thus enhancing our understanding of their pathophysiology and surely improving therapeutic strategies.

The presented method of dynamic Doppler sonographic tissue perfusion measurement allows an investigator independent measurement of color Doppler signals inside any region of interest accessible to ultrasound. All parameters of this color Doppler investigation and measurement can—and must—be standardized. The videos are recorded with a fixed preset of ultrasound machine features and are evaluated automatically. Different types of ROIs can be defined according to the user's needs as freehand, parallelogram or concentric regions and reproducible sub-regions can be defined. This leads to a highly graded appreciation of the perfusion distribution inside a tissue and allows an unprecedented detailed numerical description of the microvascular tree in a given structure.

We could demonstrate significant differences between normal and inflammatory hyperperfused bowel segments in Crohn disease [5] and ulcerative colitis, in lymphadenitis of infectious mononucleosis and Hashimoto thyreoiditis (results not shown). In inflammatory bowel diseases we found a significant correlation of histologic markers of inflammatory activity with bowel wall perfusion intensity (results not shown). We were able to differentiate perfusion intensity in tissue slices of proximal *vs* distal renal cortex [3] and could correlate perfusion data to MAG3-scintigraphy of kidneys (results not shown). We could moreover demonstrate a significant drop of perfusion in the insufficient renal transplant as well as significant loss of perfusion in renal transplants over time [2]. In tumors we could demonstrate a significant correlation of tumor oxygenation with perfusion intensity and significant differences of perfusion between lymph node metastases of different N-stages [16].

Possible applications might go far beyond the ones mentioned above. Hyperperfusion of renal parenchyma could indicate that kidneys in children are actually involved in a urinary tract infections or would differentiate renal transplant infection from rejection (own observation). Evaluation of pulsatility of small vessels could offer a tool to estimate tissue tension and stiffness of interstitial matter. Fetal and obstetrical perfusion measurements could considerably improve treatment of pregnant women and their fetuses and help to clarify intrauterine growth restriction, placenta insufficiency, infections, and malformations.

The results are a byproduct of a normal sonographic examination and are in no way an additional burden for neither the patient or the budget (there is no need for contrast media, catheter insertion or additional hardware, there is a very fast bedside examination, no need to wait for contrast enhancer influx, and no risk of adverse reaction to injected material).

Quantification of perfusion could not only help in diagnostics. Effects of therapeutic measures could be evaluated more precisely. Antiangiogenetic therapies

could be possibly monitored, antineoplastic agents could be administered according to their measured effects on their targets, anti-inflammatory therapy could be tailored and side effects (e.g. of corticosteroids) could be minimized by avoidance of overtreatment. Perfusion can now be examined precisely in any sonographically accessible tissue, thus eventually improving our understanding of the underlying pathophysiology in the individual patient at their bedside. These possible advantages could have a direct impact on further research and clinical practice. We are therefore optimistic in offering a useful method for many clinical disciplines and invite researchers to explore their own fields of application.

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