Can We Measure Renal Tissue Perfusion by Ultrasound?

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Background: Perfusion of any organ is a necessary prerequisite of its normal function and reflects disease and functional activity. Easily applicable methods to quantify tissue perfusion are therefore urgently wanted. Widely used single vessel resistance index (RI) calculations have profound conceptual and practical limitations rendering them an often unreliable tool. This paper presents the novel technique of dynamic sonographic tissue perfusion measurement (DTPM) to overcome RI's constrictions.

Basic Assumption: In contrast to using RI calculations we consider perfusion as a product of mean blood flow velocity and mean perfused vascular area inside a tissue during a complete heart cycle.

Method: Color pixels in a standardized region of interest in standardized recorded color Doppler sonographic videos are evaluated by the PixelFlux-software. Mean blood flow velocity and mean perfused area are calculated automatically image by image from the beginning to the end of a complete heart cycle. The product is the mean perfusion intensity of the entire region of interest, the pulsation of all parameters allows calculation of so called tissue pulsatility and resistance indices.

Material: DTPM is demonstrated in examples of healthy and transplanted kidneys with normal and compromised function as well as in an apparently healthy kidney from a diabetic individual.

Results: DTPM permits a more realistic appreciation of tissue perfusion compared to RI. DTPM describes quantitatively the microvascular state of the renal cortex in millimetre-thin slices. Functional and morphologic changes can be detected very early this way. Future studies have to plumb the full potential in detection and intervention in acute and chronic renal disease.

KEY WORDS — blood flow, color Doppler ultrasonography, dynamic tissue perfusion measurement, resistance index, renal, perfusion

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Why Renal Perfusion Measurement?

The abundant perfusion of kidneys [1] points to the eminent functional meaning of blood flow for these organs [2]. Changes of renal perfusion are the inevitable consequence of changes in renal function in health and disease. The way to end stage renal failure is characterized by a steady decline of

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blood flow in the kidneys. Therefore, measuring renal perfusion can greatly enhance our understanding of disease kinetics and grading in general and in the individual patient [3].

Feasibility of Sonographic Perfusion Measurement

Tissue perfusion is the passage of a certain volume of blood in a certain time through the vessels of the tissue. Color Doppler sonography (CDUS) offers all information to describe this perfusion. The perfusion volume may be perceived as a certain area perfused with a certain velocity. In CDUS, color defines both areas and (by the shading) the velocity—both are followed up in real time according to the changing hemodynamics from the beginning to the end of a heart cycle. CDUS is thus able to depict all necessary perfusion phenomena. Dynamic Tissue Perfusion Measurement (DTP) is the method to extract these data numerically.

Principles of Dynamic Tissue Perfusion Measurement (DTP)

DTP overcomes the disadvantages of certain existing methods assessing the perfusion of kidneys and other organs. This synopsis focuses on the basics of perfusion measurement of renal parenchyma, but DTP is applicable to other organs such as the bowels, thyroid, lymph nodes, liver, spleen and brain, as well as tumors.

Perfusion Intensity

To study the perfusion of branched vessel architecture it is desirable to refer to tissue perfusion instead of perfusion of single larger vessels. DTP is based on flow signals in renal vessels depicted by CDUS. It is based on the local momentary flow velocity v of the erythrocytes and the momentary area A occupied by vessels inside the Region of

Interest (ROI). With both velocity and area supplied, CDUS gives the necessary information to calculate the intensity of blood running in a given tissue plane or (in the case of 3D and 4D US) in a certain volume. The following new parameter, the so-called perfusion intensity I is crucial. It is defined by

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

where A_{ROI} is the area of the ROI (encompassing also nonperfused parts of the tissue). Conceptually speaking, the perfusion intensity covers variations of blood flow velocity and the relation of the perfused part of the ROI to the whole ROI, and is therefore a measure of the perfusion quantity of the whole ROI. In renal applications, but also in many other situations, diminished vessel density inside the renal parenchyma can be an indication for decreasing functionality due to scarring, aging, chronic disease, loss of glomeruli or nephrotoxic medication. This decrease is detected by decreasing perfusion intensity.

Periodicity

The periodicity of renal blood flow due to periodic heart action calls for evaluating the perfusion at every point during the heart cycle (Fig. 1). Hence, it is needful to work with color Doppler sonographic videos encompassing at least one full heart cycle (2 sec). A reliable tissue perfusion measurement has to refer all perfusion parameters to full heart periods.

Standardization

Standardization of image acquisition and selection of the ROI is a necessary precondition in achieving reliable measurements. This is a routine in daily practice since for a given organ (e.g. kidney) sonographers use predefined ultrasound machine settings to get the optimal image quality. Basic settings to
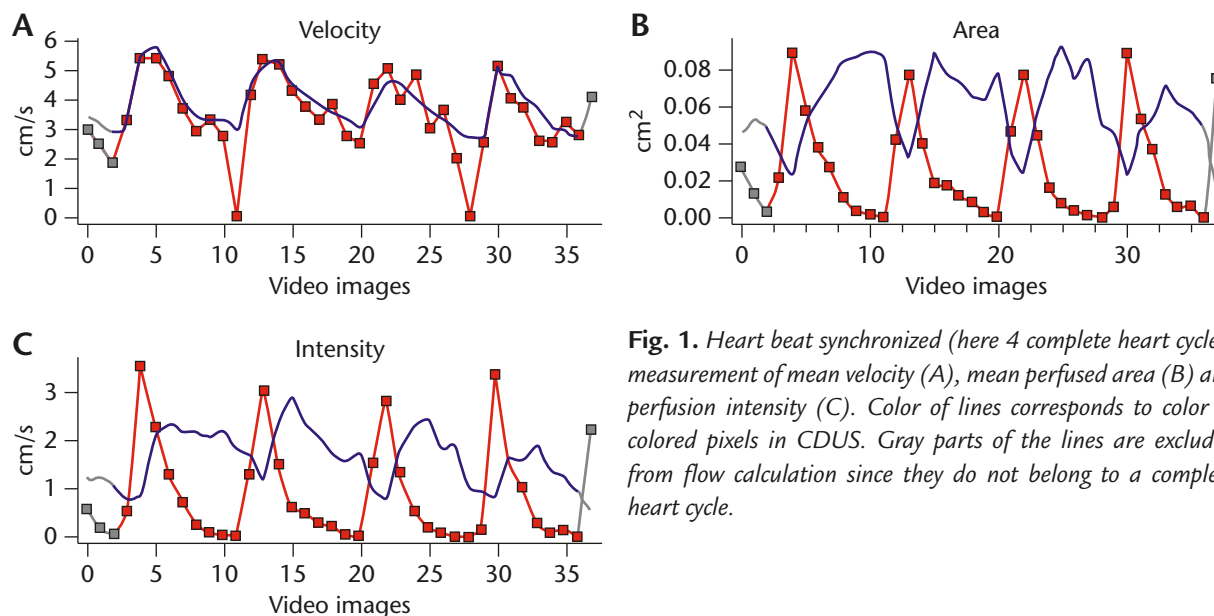
Fig. 1. *Heart beat synchronized (here 4 complete heart cycles) measurement of mean velocity (A), mean perfused area (B) and perfusion intensity (C). Color of lines corresponds to color of colored pixels in CDUS. Gray parts of the lines are excluded from flow calculation since they do not belong to a complete heart cycle.*

be kept constant are color Doppler frequency and gain. In renal application of DTP, it is moreover useful to define the ROI as a full cortical segment fed by one interlobar artery. This segment may then be subdivided into horizontal slices to calculate their perfusion intensity separately (Fig. 2). This helps describing the branching of the cortical vascular tree according to the perfusion at these different levels.

Since the color of a certain pixel defines its velocity vector (v) directed straight towards the transducer the true velocity (v_t) of the erythrocyte is given by the formula $v = v_t/\cos \alpha$ if an angle α between the vessel and the ultrasound propagation line exists. In a renal segment a strictly symmetric branching of the arcuate and interlobular arteries is given. Thus, in two dimensional Doppler sonographic videos a constant error has to be accepted. This does not hamper reliable perfusion measurements of the renal cortex since the standardization of the ROI, and the strict segmental construction of the kidney as well as the high symmetry of each segment, provide comparable measurement conditions. Thus the systematic error due to the individual angles of each interlobular vessel is negligible. Measurements in 3D and 4D color Doppler sonographic videos allow calculations which eliminate this angle problem.

Measurement Results in DTP

Perfusion intensity is by far the most important parameter derived from DTP. Table gives an overview of further interesting features in DTP.

Practical Prerequisites of DTP

Many broadly accepted methods to accomplish perfusion assessment are cumbersome, not easily accessible, invasive, ionizing or/and costly. In comparison, DTP does not require special machinery. Using standard color Doppler equipment, a short color Doppler sonographic video of 2 to 3 seconds duration is recorded. The sequence, containing at least one complete heart cycle, is evaluated by means of dedicated DTP software (PixelFlux [4]) on a standard personal computer. Thus a DTP measurement takes no more time and no special equipment compared to a conventional color Doppler sonograpic examination of the kidney.
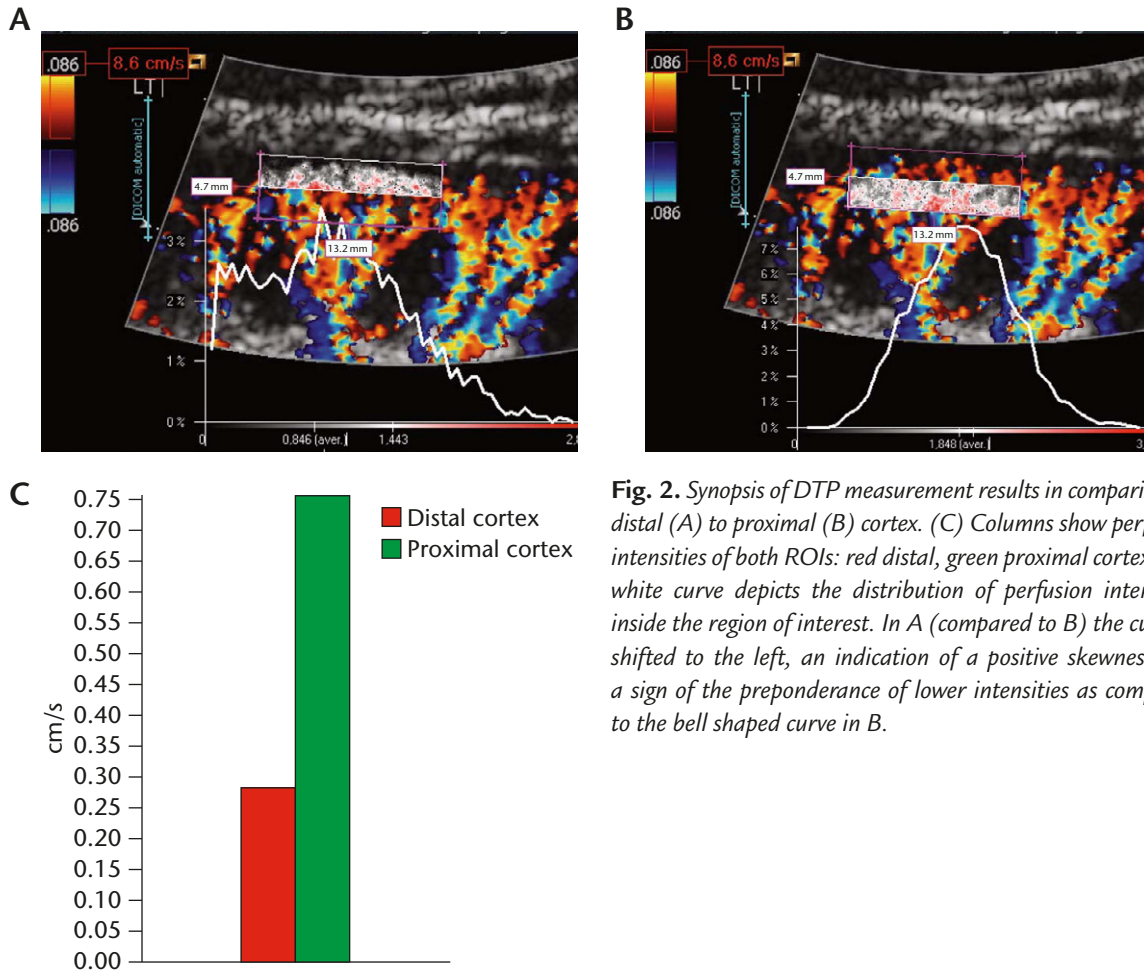
A

B

C

Fig. 2. *Synopsis of DTP measurement results in comparison of distal (A) to proximal (B) cortex. (C) Columns show perfusion intensities of both ROIs: red distal, green proximal cortex. The white curve depicts the distribution of perfusion intensities inside the region of interest. In A (compared to B) the curve is shifted to the left, an indication of a positive skewness and a sign of the preponderance of lower intensities as compared to the bell shaped curve in B.*

Advantages of DTP

DTP vis-à-vis conventional RI measurements

Nowadays RI measurements are a standard procedure in evaluating the quality of renal perfusion. Nevertheless, this time honored parameter has substantial inbuilt flaws, using only two velocity measurements during a complete heart cycle (maximum systolic and end-diastolic velocity). RI measurements refer to flow at a single point in a single vessel and most importantly do not refer to perfused area inside a tissue.

Conventional RI measurements tend to overestimate perfusion since with the loss of a cortical vessel due to scarring the neighboring vessels often react with a counteractive dilation to compensate for the loss of the vascular network. Thus a decline

of the RI in vessels which are still detectable mocks the investigator. The RI in vanished vessels cannot be measured anymore. The investigator must select from vessels which are expected to dilate in compensation thus showing an RI which is lowered. Since a low RI is uniformly attributed to a good perfusion misinterpretation of renal diseases by means of conventional Doppler interrogation may be the consequence. DTP overcomes this by evaluating all vessels inside a complete renal segment: dynamic changes of perfusion parameters are observed for larger ROIs instead of single vessels. For example, the perfusion intensity parameter introduced by DTP reflects diminished vessel density because all measurements refer to the entire segment, not only to the remaining vessels. This is a fundamental advantage over RI measurements based solely upon pointwise flow velocity measurements in a

Table. Selected parameters measured by DTP

DTP parameter, each separated for blue and red pixels (defining flow to and away from the ultrasound transducer)

    Mean perfusion velocity of the entire ROI (cm/s)

    Mean perfused area of the entire ROI (cm^2)

    Mean perfusion intensity of the entire ROI (cm/s × cm^2/cm^2)

Intensity distribution parameters

    Intensity distribution curves

    False color dynamic intensity distribution maps

    Skewness of intensity distribution

    Kurtosis of intensity distribution

Parameters describing the pulsatility of flow

    Tissue Resistance Index of velocity (TRI_v) = mean $v_{sys} - v_{dia}/v_{sys}$ of the entire ROI

    Tissue Pulsatility Index of velocity (TPI_v) = mean $v_{sys} - v_{dia}/v_{mean}$ of the entire ROI

    Tissue Resistance Index of area (TRI_A) = mean $A_{sys} - A_{dia}/A_{sys}$ of the entire ROI

    Tissue Pulsatility Index of area (TPI_A) = mean $A_{sys} - A_{dia}/A_{mean}$ of the entire ROI

    Tissue Resistance Index of intensity (TRI_I) = mean $I_{sys} - I_{dia}/I_{sys}$ of the entire ROI

    Tissue Pulsatility Index of intensity (TPI_I) = mean $I_{sys} - I_{dia}/I_{mean}$ of the entire ROI

4D parameters

    True flow volume across horizontal tissue sections (mL/s)

    Spatially angle corrected volumetric flow in distorted vessels

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few intrarenal vessels. Thus it can be expected that DTP measurements yield better and more reliable information on renal tissue perfusion.

An example of the inferiority of RI *vs.* DPT measurements is given in Fig. 3. Two renal transplants with insufficiency (upper line) and normal function (lower line) are compared both by RI measurements in three interlobar arteries, as well as by DTP in two slices of the renal cortex (proximal 50% and distal 50%). DTP demonstrates a striking loss of perfusion in the insufficient kidney. Distal perfusion is completely extinct as no perfusion signal can be detected and thus measured any longer in the distal 50% of the renal cortex. Proximal cortical perfusion is diminished to only 12% of the healthy transplant. In contrast to this clear discrimination, RI measurements tell us that both kidneys have a normal average RI of 0.66. Here, RI cannot distinguish between good and bad perfusion and overestimates the perfusion of the damaged transplant and may thus lead to wrong decisions in the individual patient.

In-depth Analysis of DTP

DTP provides completely new insights into tissue perfusion. Based on the three main parameters, velocity, area and intensity averages (see Fig. 1) as well as Tissue-RI and Tissue-Pulsatility Index (PI) for these parameters are calculated. They cannot be detected with the conventional RI and measurements which are for the time being, the unreliable basis of today's sonographic perfusion evaluation.

DTP can describe changes of microvasculature in standardized millimeter-thin slices of the renal cortex [5]. Thus, renal tissue perfusion measurements achieve an unprecedented precision. This opens many new ways to see renal diseases from a functional point of view instead of being focused on laboratory parameters and histology. From a theoretical viewpoint these commonly used decision tools need a completion by a functional method such as DTP since kidneys adapt for a very long time to the creeping loss of tissue to keep renal function at a normal level. Histological damage is a rather late result only preceded by functional damage [6]. Large changes in renal function due to ischemia can be observed within minutes [7]. Renal functional decline precedes morphologic changes of chronic allograft nephropathy [8]. Structural changes may take weeks to occur [9]. Very quick blood flow changes in the course of a disease [10] can easily be shown by DTP. DTP gives us the opportunity to be up to these changes with no time gap, which means without the delay of the creatinine-blind period.
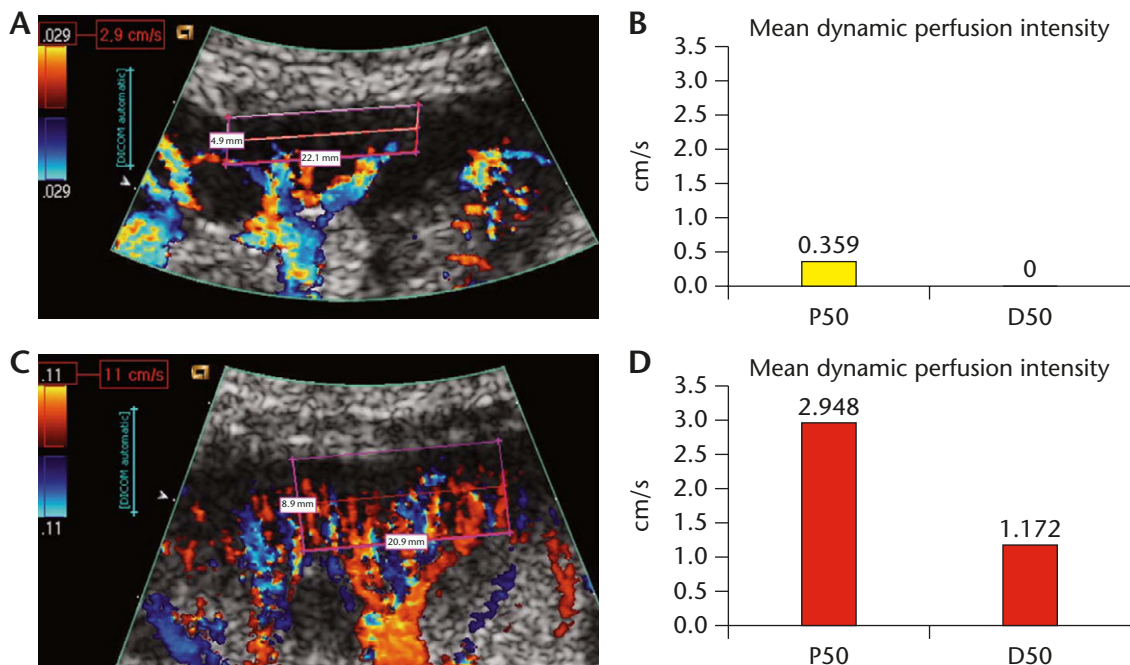
Fig. 3. *Two kidneys are investigated with identical and normal RIs of 0.66 (spectral analysis not shown). Upper line insufficient kidney (creatinine 270 µmol/L). Lower line normal kidney (creatinine 70 µmol/L). Their color Doppler sonograms show great differences of perfusion in contrary to RI. Different maximum velocities as given by the color bar are automatically recognized by the measurement software (see inset). Dynamic Tissue Perfusion measurement is able to quantify these perfusion differences which are not seen by RI measurements. P50 = proximal 50% of the cortex; D50 = distal 50% of the cortex.*

Recently, we reported on clinical application of DTP in renal [5] and bowel diseases [11], in renal transplants [12,13] and in tumors [14–16]. Within the renal cortex a significant decline of perfusion intensity from proximal to distal layers was demonstrated [5]. This corresponds to the branching of the cortical arteries only the tiniest of which reach the subcapsular region.

Inflammatory hyperperfusion is easily detected with DTP. DTP is able to measure the loss of subcapsular microvessels in kidneys quite early. In a hypertensive diabetic individual without albuminuria and normal serum creatinine DTP reveals not only a drop of perfusion intensity within the proximal 20% of the renal cortex but also an impressive shift towards smaller intensities compared to a healthy kidney with a mirror-inverted distribution of intensities in the same ROI (Fig. 4). DTP introduces the parameters skewness and kurtosis into the sonographic evaluation of tissue perfusion. Figures 2 and 4 give impressive examples of the discriminating power of both of these parameters.

In Fig. 2 mapping of flow intensities in false colors shows the flow intensity distribution over time in the entire ROI showing the distal 50% (upper image and red column) and the proximal 50% of a complete renal cortical segment (lower image and green column). The intensity distribution curves show clearly distinguishable differences of both ROIs—a left shifted curve pointing to the predominance of lesser intensities in the spectrum of all vessels inside distal cortex, versus a bell shaped distribution of flow intensities in the proximal cortex thus pointing to a balanced distribution of intensities inside the vascular bed of this ROI. A skewness above zero describes a right-skewed distribution, i.e. the mass of the distribution is concentrated on the left side of the curve. In this example the skewness of the distal cortical perfusion intensity is nearly twice compared to the proximal cortex. The kurtosis also shows clear differences reflecting the differences in the distribution curve. A distribution with positive kurtosis (leptokurtic) has a more acute peak around the mean.
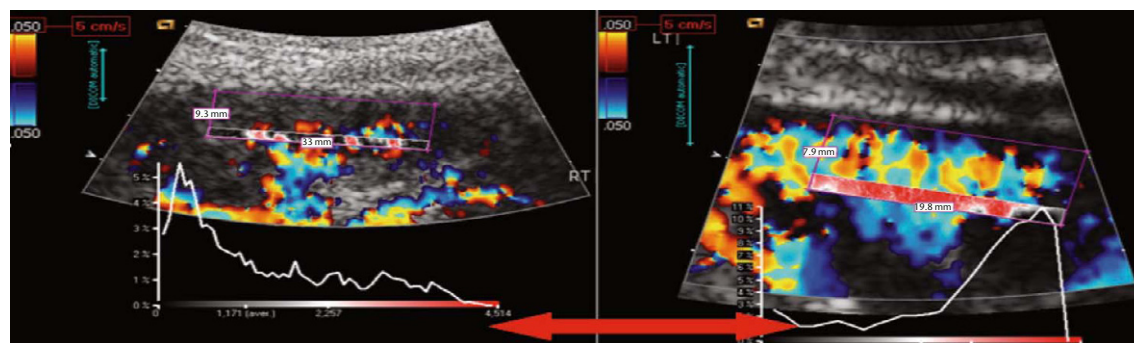
Fig. 4. *Comparison of DTP in an apparently healthy diabetic kidney (left) and a healthy control (right).*

A higher positive value describes a sharper peak of the curve. The amount of blood passing through the tissue section of the same size is three times higher in the proximal cortex (green column *vs.* red column).

In Fig. 4 DTP demonstrates its potential to reveal microvascular renal damage in diabetes even if no other test is able to detect it. Perfusion intensity of the apparently healthy kidney of a diabetic patient is only 25% of the healthy counterpart in the proximal 20% of the cortex. But no less impressive are the different shapes of the intensity distribution curves. They demonstrate clearly the dramatic shift towards less perfused cortical vessels in an asymptomatic diabetic kidney (left) compared to a normal kidney (right) under exactly identical imaging conditions. Skewness is positive in the diabetic kidney and negative in the healthy control.

In renal artery stenoses the impact of stenoses onto the parenchymal perfusion can now be measured at site. Restenoses can be better evaluated according to their effect on cortical perfusion. Our own investigations (unpublished results) showed that in the course of a progressive renal disease, a functional adaptation can be demonstrated by DTP before the creatinine clearance starts declining into renal insufficiency.

In renal transplants as early as 1 year after renal transplantation a significant drop of cortical perfusion was found [12]. In a parallel a rise of the entire ROI's perfusion pulsatility was demonstrated [13]. This needs to be further investigated in histologically proven studies. Thus DTP offers broad access

to a refined physiological evaluation of the actual state of a kidney.

Perspective

The effect of therapy on a renal disease might be controlled by DTP. In all chronic kidney diseases, which are known to end up uniformly in scarring and vessel loss [17–20], these tiny vessels are expected to disappear first. Thus DTP might help to follow up the perfusion of this sensitive vascular bed. The hope is to detect diabetic microvessel disease noninvasively long before manifestation. Interventions at renal arteries can be estimated according to their effect on the cortical perfusion. DTP can investigate kidney perfusion, separately for each side but also separately for sub regions of the kidney. This might help to plan operations.

A rarely investigated situation is the effect of venous outflow obstruction on renal function. We could demonstrate a significant decline of left renal perfusion in the so called *nutcracker phenomenon* of the left renal vein accompanied by a variety of symptoms disappearing as a consequence of medical treatment leading to an improved perfusion of the left kidney [21]. Symptoms related to renal diseases can be now evaluated with respect to the changes of kidney perfusion. The hope is firstly to determine a given symptom as of really renal origin and secondly to study the effect of therapeutic interventions with respect to these symptoms. The connection of symptoms to renal perfusion might

be exhibited by DTP. The use of DTP can establish individual perfusion profiles in the time course of a renal disease and may help tailor an individual approach to renal diseases.

Conclusion

It can be concluded that by means of color Doppler sonographic Dynamic Tissue Perfusion Measurement a valuable tool has emerged. It provides sound physiological data to determine the functional situation of an individual kidney. This should open new doors to alleviate the fate of renal patients and to retard or even prevent the so far fatal course of many renal diseases.

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