

THE STUDY OF ENDOTHELIAL FUNCTION IN CKD: IS DIGITAL PLETHYSMOGRAPHY A RELIABLE SURROGATE OF FLOW MEDIATED VASODILATION IN THE BRACHIAL ARTERY IN THE FOREARM?

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Introduction and aims

Chronic Kidney Disease (CKD) is condition considered at very high risk for endothelial dysfunction. Methods for evaluating endothelial function include the nitric oxide (NO) dependent flow-mediated dilation (FMD) in the brachial artery in response to forearm ischemia (measured by high resolution Ultra Sound, US) which is considered a gold standard technique, and the Reactive Hyperemia Index (RHI) in response to digital ischemia measured by plethysmography (Endo-pat 2000 - ITAMAR). These two tests are linearly related in the general population [Am Heart J. 2003; 146: 168-74]. The Endo-Pat system is held as a valid surrogate of FMD by high resolution US and being simpler and more rapid to apply, it is increasingly used in clinical research. However, the reliability of this method for assessing endothelial function in CKD patients has never been investigated.

Patients & Methods

We compared the two methods in an incident series of eighty-eight patients with stage 3-5 CKD who participated into a randomized clinical trial aimed at assessing the effect of an active form of vitamin D, paricalcitol, on endothelial function (PENNY. clinicaltrials.gov identifier: NCT01680198; Hypertension 2014;64:1005-11). Their mean age was 63±11 years (65% males, 35% diabetics). Specific normative data for Flow Mediated Vasodilatation were obtained by a national registry of healthy subjects studied at centers participating into a national study that standardized the technique at 7 Italian centers (J Hypertens. 2012;30:1399-405). The lower limit of the normal range for digital reactive hyperemia was 1.67 (Endopat-manufacturer information).

Results

At baseline, all but one CKD patient (n=87; 99%) had reduced Flow Mediated Dilatation (i.e. an increase in FMD <12%) of the brachial artery whereas only ten patients (11%) had a reduced Reactive Hyperemia Index at digital plethysmography (<1.67) indicating a substantial dissociation between FMD and RHI (kappa statistics: 1%, $r = -0.05$, $P = 0.63$ [Fig.1]). As expected, FMD was inversely related with age ($r = -0.29$, $P = 0.007$) which specifically confirms in CKD patients a phenomenon observed in other conditions and population-based studies, while unexpectedly RHI wasn't ($r = 0.06$, $P = 0.60$).

During the clinical trial paricalcitol as compared to placebo induced a 61% increase in FMD after 12 weeks of treatment [Fig.2] and such an effect disappeared 2 weeks after stopping paricalcitol. In contrast, paricalcitol treatment had no effect on the digital reactive hyperemia index [Fig.3].

Figures

Fig.1

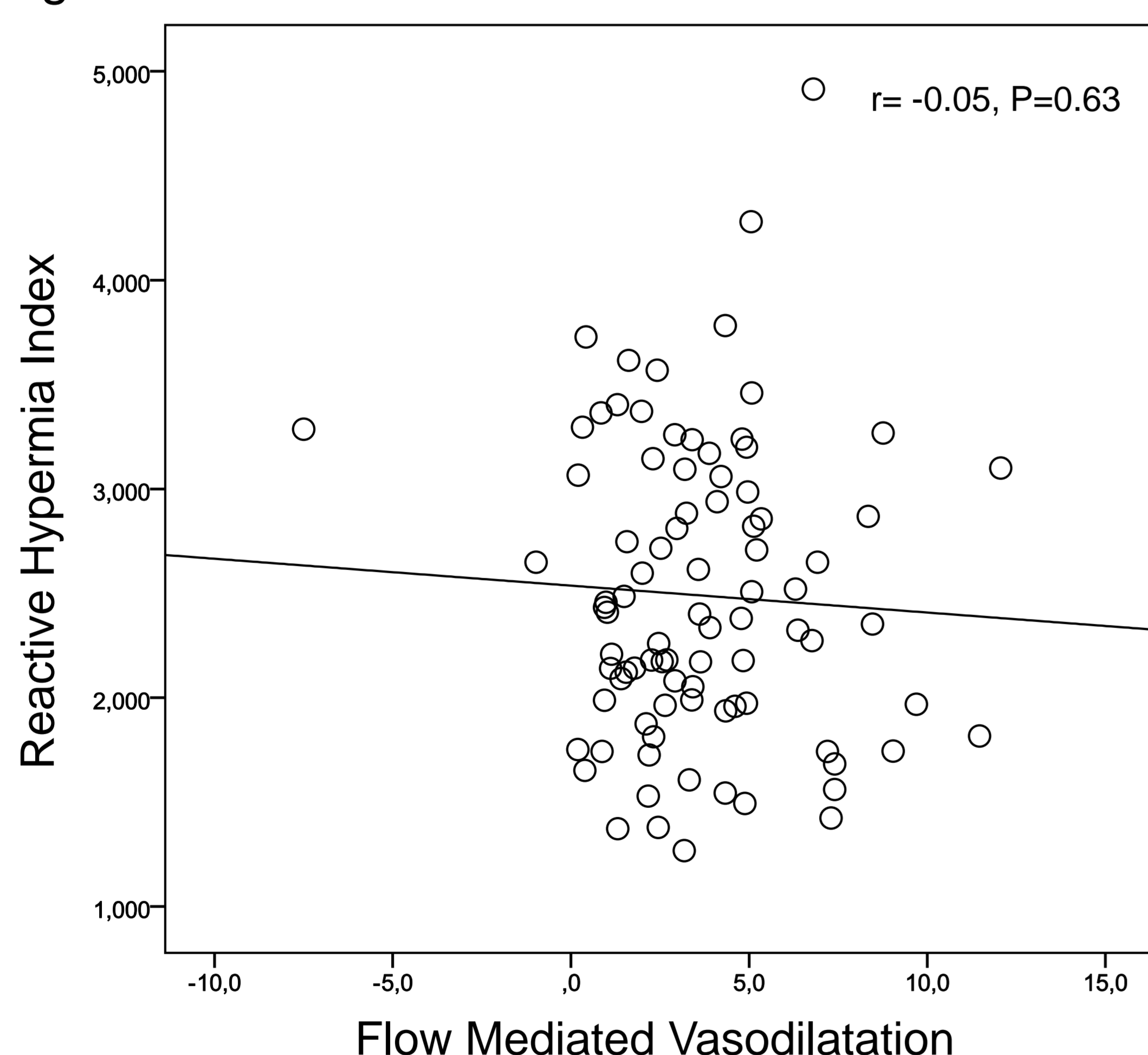


Fig.2

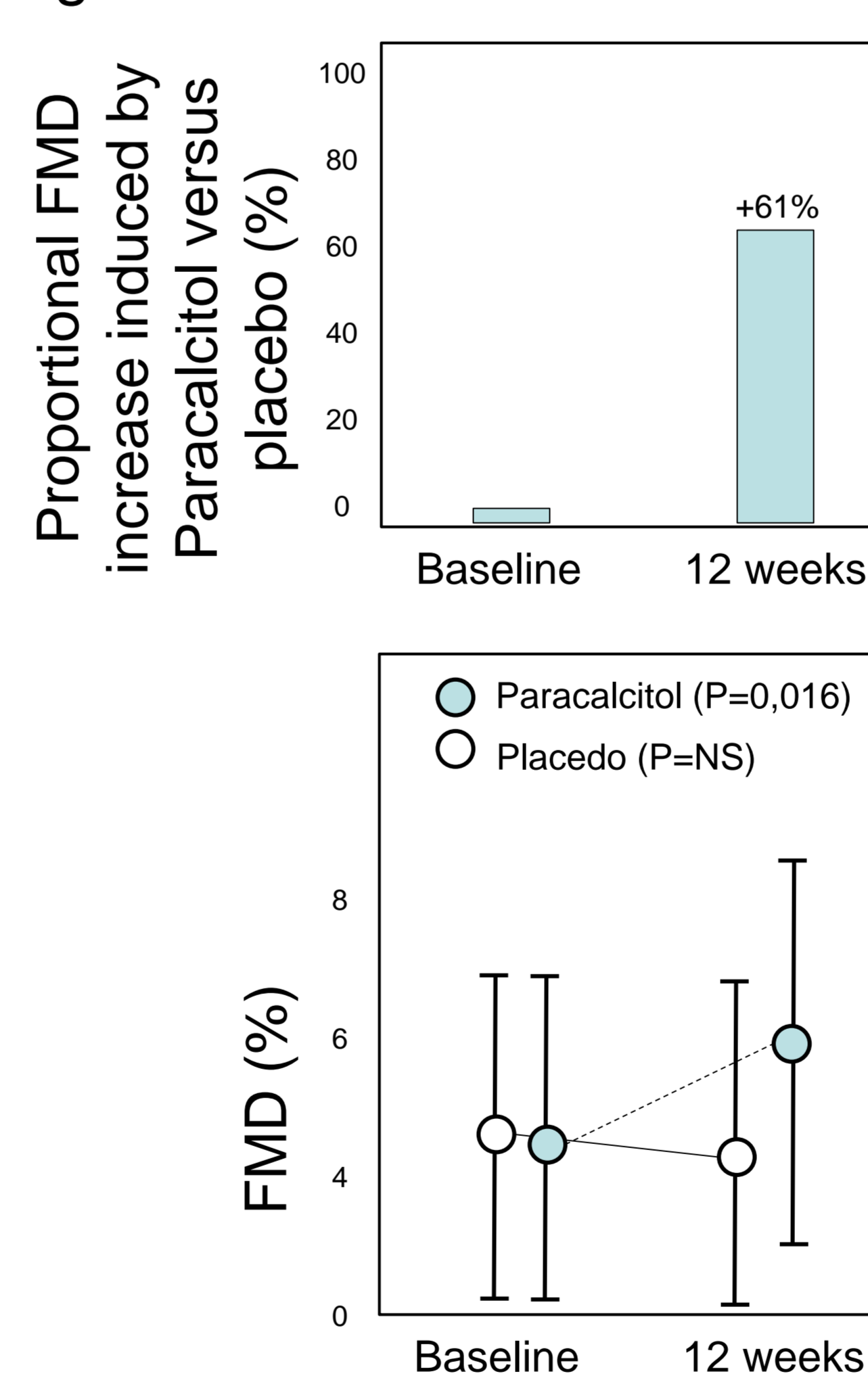
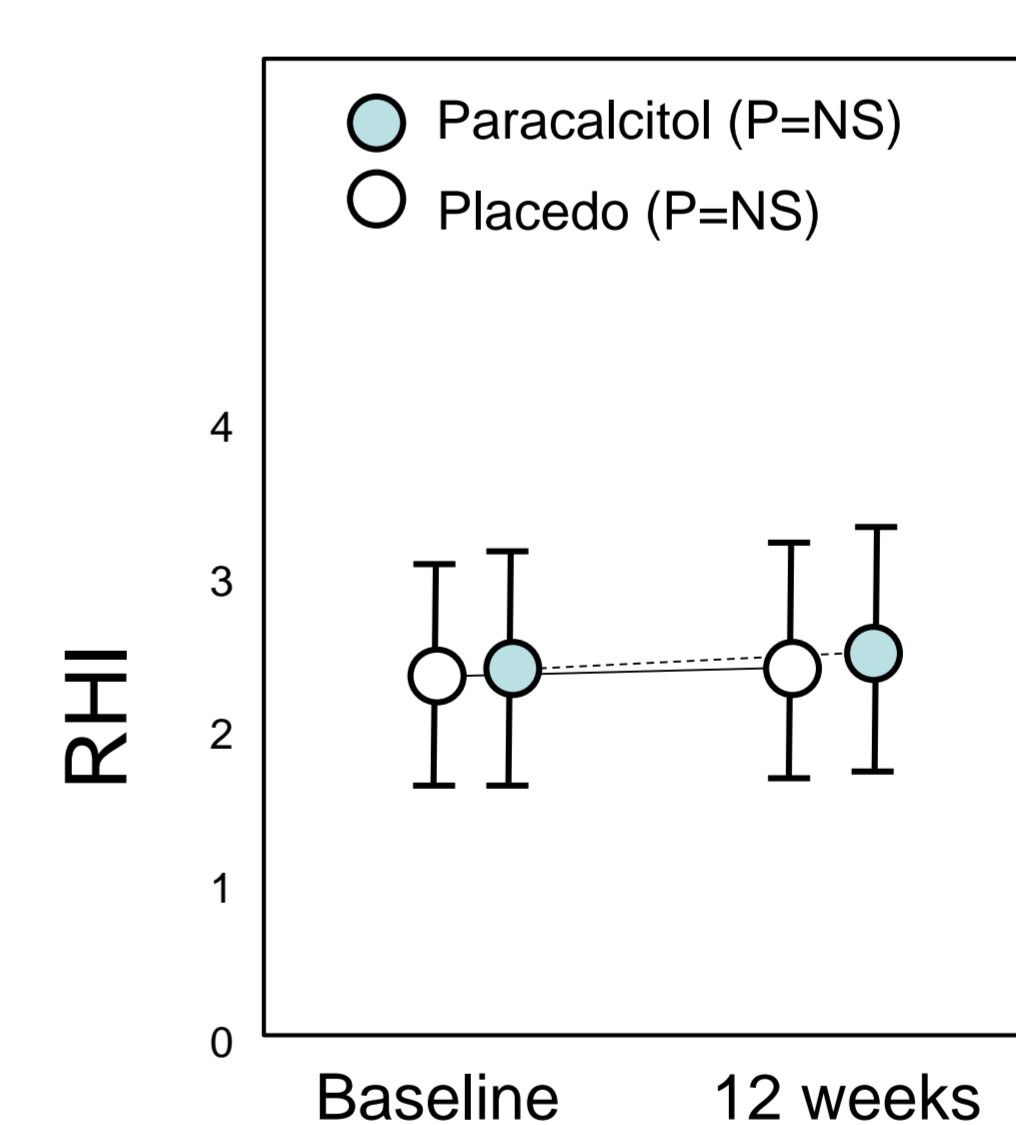


Fig.3



Conclusions

Endothelial dysfunction is a pervasive phenomenon in CKD when assessed by a gold standard technique like FMD measured by high resolution US. However, this alteration is rarely detected by the application of digital Reactive Hyperemia Index of the Endo-Pat system and the same system fails to capture meaningful endothelium-mediated responses to drugs like paricalcitol in CKD patients. These observations indicate that the study of endothelial function in CKD demands the application of gold standard techniques like FMD by high resolution US. Surrogate measurements like Endo-Pat by now are overtly inadequate for clinical research and clinical practice in CKD patients.

