First experience with renal denervation in the real life

About 6 cases treated with Vessix balloon, Boston scientific

Dr PEYRE Jean-Pascal
Private hospital Marseille Beauregard
MEET, Nice 2014
ONE CASE PRESENTATION

• **MR MRKT** : 56 YO

• RESISTANT severe hypertension treated with 6 anti-hypertensive medications since 2010

• No etiology of hypertension

• cardiovascular risk factor :
  - ∅ tabagism
  - ∅ hyperlipidemia

• MAPA/24H : 186/102 mmhg, no dipper
Preparation

- General anesthesia with propafenone (abdominal pain during the radiofrequency)
- Controlled ventilation with laryngeal mask
- Injection before radio frequency of 2500 unit of unfractioned heparin
- 30 s of low inflation balloon (3 atm)
- Duration of complete procedure: 30 minutes
Femoral approach with 8F catheter

Selective injection with femoro-renal catheter 4F No renal stenosis
QCA quantification of renal artery size

<table>
<thead>
<tr>
<th>Total segments analysés</th>
</tr>
</thead>
<tbody>
<tr>
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<table>
<thead>
<tr>
<th>Diamètre</th>
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<table>
<thead>
<tr>
<th>Zone</th>
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<table>
<thead>
<tr>
<th>Patient</th>
<th>MKRTHYAN, KHACHIK</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID</td>
<td>129941-201307161247298</td>
</tr>
</tbody>
</table>

| Né(e) le : | 18/04/1957 |
| Médécin :  | Dr CHARMASON,... |
| Hôpital   : | Hopital Prive Beauregard |
| Date exam : | 16/07/2013 |

<table>
<thead>
<tr>
<th>Segment</th>
<th>Nom étude</th>
<th>Opération</th>
<th>ID séq.</th>
<th>N° d'image</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Diam.</th>
<th>Zone</th>
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<tbody>
<tr>
<td>mm</td>
<td>mm²</td>
</tr>
</tbody>
</table>

| Min.  | 5.47 | 23.54 |
| Max.  | 7.25 | 41.29 |
| Moy.  | 6.40 | 32.26 |
| Ec type | 0.41 | 4.12 |

| Long. segment analysé | 39.36 mm |

<table>
<thead>
<tr>
<th>Contour corrigé</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00 Guche</td>
</tr>
<tr>
<td>0.00 Droit</td>
</tr>
<tr>
<td>0.00 Total</td>
</tr>
</tbody>
</table>

Dr PEYRE Jean-Pascal
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MEET, Nice 2014
0.018 wire cross the artery and balloon inflation with Vessix 3 atm 30 s

LEFT RENAL ARTERY

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RIGHT RENAL ARTERY
FINAL INJECTION AND femoseal femoral closure
POST DENERVATION RESULTS

At 6 month : diminution of 2 anti-hypertensive medications

MAPA/24h : 148/86

Dipper patient
6 cases treated with Vessix during 2013 and 2014

- All patients had severe resistant hypertension treated with 4 anti-hypertensive médications or more
- Patients had systolic blood pressure higher than 160 mm Hg at the visit or MAPA
- 3 males et 3 females / we have no data for one patient
- 2 patients had MAPA before and after renal denervation
Success / complications

- 100 % technical success
- No complication
All patients (5) decrease systolic blood pressure at 6 month

- Réduction in systolic blood pressure at least of 20 mm Hg
- reduction of anti-hypertensive medications number for 4 cases. One case remind unchanged.
For 2 patients, we have MAPA before and after 6 month

Réduction in systolic blood pressure at least of 20 mm Hg

= 50% reduction of cardiovascular risk

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Reduction of anti-hypertensive medications at 6 month

- Number of anti-hypertensive medication before
- Number of anti-hypertensive medication at 6 month

60% reduction of anti-hypertensive medications in 4 cases

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Conclusion

- We have presented a small number of patients treated with Vessix for essentiel severe resistant hypertension in the real life.

- The use of Vessix was SAFE, with 100% of procedural success and no complication.

- We have selected very severe patients with resistant hypertension over than 160 mm Hg with 4 anti-hypertension medications or more (in accordance with recommendations).

- 100% of patients have had at least a reduction of 20 mm Hg in systolic blood pressure at 6 month.

- 80% of patients have decreased of 60% the number of anti-hypertension medications.
Heart rate variability and renal denervation with Vessix

preliminary results

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Dr MACALUSO Gilles
Private hospital Marseille Beauregard
MEET, Nice 2014
Heart rate variability

• heart rate variability can be the reflection of sympathetic and parasympathetic tonus

• We have analyzed heart rate variability on 4 patients before and one day after renal denervation and six month later

• We will present results for the first patient we have analyzed before and 24 hours after denervation with Vessix Balloon

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Criteria analyzed during 24 hours monitoring

- temporal: parasympathetic tonus
  - PNN50
  - PNN30
  - RMSSD
- spectral:
  - HF (high frequencies 0.15 - 0.40 Hz): parasympathetic tonus
  - LF (low frequencies 0.0033 - 0.09 Hz): sympathetic tonus or increase of parasympathetic tonus + SRAA
Temporal analyze of 24 hours

BEFORE RD

24H after RD

- PNN50 (%)
  - BEFORE RD: 2
  - 24H after RD: 4
  - Increase: +90%

- PNN30 (%)
  - BEFORE RD: 9
  - 24H after RD: 15
  - Increase: +71%

- RMSSD (ms)
  - BEFORE RD: 21
  - 24H after RD: 24
  - Increase: +18%

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Dr MACALUSO Gilles
Private hospital Marseille Beauregard
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Temporal analyze night and day

**Day**

- **BEFORE RD**
  - PNN50: 1
  - PNN30: 4
  - RMSSD: 16
- **24H after RD**
  - PNN50: 3
  - PNN30: 13
  - RMSSD: 23

**Night**

- **BEFORE RD**
  - PNN50: 4
  - PNN30: 5
  - RMSSD: 15
- **24H after RD**
  - PNN50: 25
  - PNN30: 26
  - RMSSD: 26

**Percentage Changes**

- **Day**
  - PNN50: +500%
  - PNN30: +225%
  - RMSSD: +43%
- **Night**
  - PNN50: +19%
  - PNN30: +9%
  - RMSSD: +1%
Spectral analyze of 24 hours

BEFORE RD  24H after RD

HF (ms²)  LF (ms²)

0 154  154 +54%  238  3018  3 931 +30%

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Dr MACALUSO Gilles
Private hospital Marseille Beauregard
MEET, Nice 2014
### Spectral Analyze of Night and Day

**Day**

<table>
<thead>
<tr>
<th></th>
<th>BEFORE RD</th>
<th>24H after RD</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>77</td>
<td>203</td>
<td>+62%</td>
</tr>
<tr>
<td>LF</td>
<td>2,721</td>
<td>3,897</td>
<td>+43%</td>
</tr>
</tbody>
</table>

**Night**

<table>
<thead>
<tr>
<th></th>
<th>BEFORE RD</th>
<th>24H after RD</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td>245</td>
<td>277</td>
<td>-7%</td>
</tr>
<tr>
<td>LF</td>
<td>3,902</td>
<td>3,628</td>
<td></td>
</tr>
</tbody>
</table>

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Dr. Peyre Jean-Pascal  
Dr. Macaluso Gilles  
Private Hospital Marseille Beauregard  
MEET, Nice 2014
The 3 other cases we have analyzed showed the same changes in heart rate variability.
Conclusion: heart rate variability changes 24 hours after renal denervation with Vessix

- We first describe a global increase of parasympathetic tonus immediately after renal denervation, especially during the day, and less during the night.
- Moderate decrease of the sympathetic tonus during the night.
- We cannot conclude for the sympathetic tonus during the day because the elevation of the low frequencies can be explained by the elevation of the parasympathetic tonus or SRAA.

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Dr MACALUSO Gilles
Private hospital Marseille Beauregard
MEET, Nice 2014
Thank you for your attention

Dr PEYRE Jean-Pascal
Dr MACALUSO Gilles
Private hospital Marseille Beauregard
MEET, Nice 2014
### 24 hours analyze

<table>
<thead>
<tr>
<th></th>
<th>before RD</th>
<th>24 hours after RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNN50 (%)</td>
<td>2.28</td>
<td>4.35</td>
</tr>
<tr>
<td>PNN30 (%)</td>
<td>8.71</td>
<td>14.98</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>20.55</td>
<td>24.42</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>154</td>
<td>238</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>3018</td>
<td>3931</td>
</tr>
</tbody>
</table>

*Results for one patient, Mr MAM.*
Results for one patient, Mr MAM.
Night analyze

<table>
<thead>
<tr>
<th></th>
<th>before RD</th>
<th>24 hours after RD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNN50 (%)</td>
<td>4.46</td>
<td>4.32</td>
</tr>
<tr>
<td>PNN30 (%)</td>
<td>14.51</td>
<td>15.90</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>25.31</td>
<td>25.68</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>245</td>
<td>277</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>3902</td>
<td>3628</td>
</tr>
</tbody>
</table>

Results for one patient, Mr MAM.
Is there a future for renal denervation after simplicity HTN-3?

Conclusions

This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLICITY HTN-3 ClinicalTrials.gov number, NCT01418261.)
HTN-3: the included patients have a resistant hypertension SEVERE?

- Patients screened:

  - systolique blood pressure > 160 mm Hg with conventionnel measurement and 3 or more anti hypertension medication (mean 5): OK

  - MAPA: systolic blood pressure > 135 mm Hg ??

  - ALL PATIENTS HAVE REALLY SEVERE RESISTANT HYPERTENSION?

    - on the number of medications (mean 5): yes

    - on the MAPA result: I don’t know (« automated 24-hour ambulatory blood-pressure monitoring was performed to ensure a systolic blood pressure of 135 mm Hg or higher »)
HTN-3 population

- race: 25% of black patients

- Renal denervation is modulate the sympathetic activity (diminution of norepinephrine and MSNA - muscle sympathic nerve activity - Dagmara Hering, Hypertension 2013;61:457-464)

- Hypertension in black patients is not a «sympathic» hypertension and black people could not be good candidate for renal denervation
HNT-3 is a renal denervation with Medtronic unipolar catheter.

Are all denervation devices equivalents for renal denervation?
HTN-3

- Catheter: medtronic
- Unipolar
- 3D denervation point by point without cartography
- Duration > 35 minutes
Vessix

• Balloon with 6 bipolar electrodes
• good reproducibility
• rapidity of the denervation (30s)
• Best quality of denervation?
Symplicity HTN-3

• Present denervation results with Medtronic ablation unipolar catheter

• On selected severe resistant hypertension patients with MAPA > 135 mm Hg which can be low for severe resistant hypertension people. No more MAPA data in the study

• with 25% of black people whose sensitivity to sympathetic blockers is poor for the treatment of hypertension

**Shows no efficacy of renal denervation**

**Can we conclude the same with all devices? An for which patients?**
NO RANDOM STUDY DATA WITH VESSIX INCLUDING MAPA

ONLY DATA FROM REGISTRY WITH GOOD RESULTS ON RESISTANT SEVERE HYPERTENSION
WE NEED TO PROGRESS IN RENAL DENERVATION

- IN the selection of good candidates: really resistant severe hypertension with MAPA > 160 mm Hg
- IN electrophysiologic or biologic markers
  - to determine the good candidates: with high level of sympathetic activity
  - to quantify the efficacy and the level of renal denervation
- IN technic denervation
How to denerve?

- longitudinal denervation (blue)
- transversal denervation (red)
We need to improve this technology, this potential therapy, and Vessix can participate to this improvement.

Today, only severe resistant hypertension patients can be candidates for Vessix denervation.
Anatomie Nerveuse Rénale

- Les nerfs naissent de D10-L2
- Les nerfs se ramifient autour de l’artère et se situent principalement dans l’adventice
Influx afferents et efferents

Vasoconstriction
Athérosclérose

Résistance à l'insuline
Troubles du sommeil

Nerfs Afférents Rénaux

Hypertrophie
Arythmie
Consommation d'oxygène

Libération Rénine → activation RAAS
Rétenion Sodium
Flux sanguin rénal
Principe : modulation des échanges nerveux entre rein et cerveau

- Destruction localisée par radiofréquence des nerfs rénaux cheminant dans l’adventice des artères rénales
- Atténuation des influx afférents et efférents entre le cerveau et le rein
  - diminution de l’activité sympathique
  - diminution de l’activité du système RAA
dernervation

- Diminution du taux de norepinephrine
- Diminution du MSNA (muscle sympathetic nerve activity)  *Dagmara Hering, Hypertension 2013;61:457-464*
<table>
<thead>
<tr>
<th>Renal Denervation Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy</strong></td>
</tr>
<tr>
<td>RF Monopolar</td>
</tr>
<tr>
<td>RF Monopolar</td>
</tr>
<tr>
<td>RF Monopolar</td>
</tr>
<tr>
<td>RF Bipolar</td>
</tr>
<tr>
<td><strong>Catheter Design</strong></td>
</tr>
<tr>
<td>Catheter with single electrode</td>
</tr>
<tr>
<td>Basket with four electrodes</td>
</tr>
<tr>
<td>Balloon with helical electrode and irrigation</td>
</tr>
<tr>
<td>Balloon with four to eight electrode pairs</td>
</tr>
<tr>
<td><strong>Guidewire</strong></td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>0.014” (0.36 mm)</td>
</tr>
<tr>
<td>0.014” or 0.018” (0.36 mm or 0.46 mm)</td>
</tr>
<tr>
<td><strong>Denervation Time</strong></td>
</tr>
<tr>
<td>2 min</td>
</tr>
<tr>
<td>6 min</td>
</tr>
<tr>
<td>2 min</td>
</tr>
<tr>
<td>30 sec</td>
</tr>
<tr>
<td><strong>Total Denervation Time</strong></td>
</tr>
<tr>
<td>35 min</td>
</tr>
<tr>
<td>24 min</td>
</tr>
<tr>
<td>4 min</td>
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<tr>
<td>1 - 2 min</td>
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</tbody>
</table>

*None of these devices are available for sale in the US.*

*Medtronic Presentation;*  
*St. Jude Website;*  
*Covidien (Maya) Presentation*  
*ReCor Presentation*  
*The Vessix™ Renal Denervation System is not available for sale in the US.*
HTN-3

- 25% de patients de race noire
- HTA du sujet de race noire est moins sensible aux bloqueurs sympathiques
• Donne des résultats négatifs avec le système Medtronic par sonde unipolaire

• Sur une population de patients dont la sévérité de l’HTA n’est par documentée sur la MAPA pré ablation (« automated 24-hour ambulatory blood-pressure monitoring was performed to ensure a systolic blood pressure of 135 mm Hg or higher »)

• 25% de sujets de race noir, moins sensibles aux traitements sympatholytiques que les caucasiens
Candidat idéal en 2014 pour la denervation

- Patient avec une hyper activité sympathique « inhabituelle »

HTA essentielle persistante severe documentée, traitée selon les recommandations avec TAS MAPA > 160 mm Hg
Les systèmes et les techniques de denervation ne sont probablement pas égaux entre eux

Les protocoles d’ablation ne sont probablement pas optimisées
« Sait-on denerver ? »
Combien détruire pour moduler efficacement?
Quels marqueurs ?

Avant l’ablation : pas de marqueur en dehors de l’HTA severe résistante

- Documenter l’hyperactivité sympathique
- Trouver un potentiel rénal d’hyperactivité sympathique

Pendant l’ablation :

- marqueur electrophysiologique d’efficacité de la denervation ?
Modèle du rein totalement dénervé

Le BI-NEPHRECTOMISE GREFFE sans les immunosupresseurs
The heterogeneous and delayed course of blood pressure normalization in hypertensive patients after bilateral nephrectomy with and without subsequent renal transplantation

Schwarz ER1, Heintz B, Stefanidis I, vom Dahl J, Sieberth HG

Ren Fail. 2000;22(5):591-604

• 14 patients dialyses hypertendus severes (TAS 175)

• 10 patients nephrectomie unilaterale dans un premier temps : augmentation de la TAS (185)

• Puis Bi nephrectomie pour les 14 patients

• Puis greffe renale pour 6 d’entre eux
EVOLUTION DE LA TAS APRES NEPHRECTOMIE

**NEPHRECTOMIE SIMPLE**

- **BASE**: 175
- **POST NEPHRECTOMIE**: 185

- 10 patients

**BI NEPHRECTOMIE**

- **BASE**: 175
- **M3**: 159
- **M6**: 149

- 14 patients
EVOLUTION DE LA TAS DES BI NEPHRECTOMISES GREFFES ET NON GREFFES

Greffes (6 patients)

Remontée de la TA après greffe

Immunosuppresseurs ?

Non greffes (9 patients)
La question n’est pas de dire la denervation marche pas, mais pourquoi HTN-3 ne donne pas de résultats
Candidats à la denervation renale

- Hypertendu avec forte activité sympathique
- hypertendu severe ....