Cerebral blood flow: possible hemodynamic links between atrial fibrillation and cognitive decline

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Atrial fibrillation (AF)
- Common arrhythmia: irregular and faster beat;
- 33.5 million people worldwide in 2010 (to be doubled in 40 years);
- Disabling symptoms and reduced quality of life;
- $ 6.65 billion/year in the USA (2006);
Background & State of the Art

- **Atrial fibrillation (AF)**
  - Common arrhythmia: irregular and faster beat;
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- **Dementia**
  - Neurological degeneration: loss of memory, socio-cognitive alterations;
  - 81 million people worldwide in 2040;
  - Healthcare burden: 2 trillion $ worldwide (2030);
  - Common risk factors with AF (e.g., age);
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  - 81 million people worldwide in 2040;
  - Healthcare burden: 2 trillion $ worldwide (2030);
  - Common risk factors with AF (e.g., age);

- Recent independent **association** between **AF** and **dementia**
  ⇒ Potential **hemodynamic mechanisms**: microembolisms, altered cerebral blood flow, hypoperfusion and microbleeds.
Background & State of the Art

Open Questions
- Linking mechanisms between AF and dementia;
- Consequences of AF rate/rhythm control on cognitive decline;
- Lacking clinical measures in the cerebral microcirculation.

Modeling approach for the cerebral hemodynamics during AF

Anselmino et al., Sci. Rep., 2016; Scarsoglio et al., J. R. Soc. Interface, 2017; Scarsoglio et al., Chaos, 2017

⇒ Impact of heart rate (HR) during AF on cerebral hemodynamics

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Heart rate response during AF on cerebral hemodynamics

Spectrum of macro- to micro-cerebral injuries from AF (Jacobs et al., 2015)
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⇒ Impact of heart rate (HR) during AF on cerebral hemodynamics
Methods: Computational algorithm

- Stochastic RR beating extraction & validated lumped modeling;
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- Mean HR = 50, 70, 90, 110, 130 bpm;
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- Stochastic RR beating extraction & validated lumped modeling;
- Mean HR = 50, 70, 90, 110, 130 bpm;
- NSR (normal sinus rhythm, blue) and AF (red);
Stochastic RR beating extraction & validated lumped modeling;
Mean HR = 50, 70, 90, 110, 130 bpm;
NSR (normal sinus rhythm, blue) and AF (red);
5000 cardiac cycles (RR beats) simulated for each configuration.
Artificially extracted beating RR reproducing in vivo ECG
⇒ higher variability and reduced correlation in AF;
Artificially extracted beating RR reproducing in vivo ECG ⇒ higher variability and reduced correlation in AF;

Lumped modeling at glance
- Fluid dynamics variables: pressure P, volume V, flow rate Q;

Network of resistances → viscosity, compliances → elasticity, inductances → inertia.

Governing equations for each region:
- Continuity equation
- Momentum equation
- Constitutive relation between P and V

Baroreceptor, autoregulation, and CO$_2$ reactivity mechanisms;

Focus on the proximal-to-distal pathway (left side):
- Large arteries (P$_a$, P$_{MCA}$, left, Q$_{ICA}$, left, Q$_{MCA}$, left);
- Distal arteries (P$_{dm}$, left, Q$_{dm}$, left);
- Capillary-venous circulation (P$_c$, Q$_{pv}$).
Methods: RR building and lumped modeling features

- **Artificially extracted beating RR** reproducing in vivo ECG
  ⇒ higher variability and reduced correlation in AF;

- **Lumped modeling at glance**
  - Fluid dynamics variables: pressure $P$, volume $V$, flow rate $Q$;
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- **Continuity equation**

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- **Constitutive relation between $P$ and $V$**

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- **Focus on the proximal-to-distal pathway** (left side):
  - Large arteries \((P_a, P_{MCA, left}, Q_{ICA, left}, Q_{MCA, left})\);
  - Distal arteries \((P_{dm, left}, Q_{dm, left})\);
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- Large arteries ($P_a, P_{MCA,left}, Q_{ICA,left}, Q_{MCA,left}$);
- Distal arteries ($P_{dm,left}, Q_{dm,left}$);
- Capillary-venous circulation ($P_c, Q_{pv}$).
Methods: Data analysis

- Percentile evaluation

(a) Percentile evaluation of cerebral perfusion pressure in patients with normal sinus rhythm (NSR) and atrial fibrillation (AF).

(b) Comparative analysis showing a higher occurrence of extreme events in AF patients compared to NSR patients. In (b), 95% of the population is represented.
Methods: Data analysis

- **Percentile evaluation**

- **Recurrence of extreme events (hypoperfusions and hypertensive events) in AF**
Results: proximal-to-distal pathway

Heart rate response during AF on cerebral hemodynamics
Results: proximal-to-distal pathway

HR=70 bpm. Compared to NSR, AF triggers a higher variability of the cerebral hemodynamic variables, increasingly proceeding towards the distal circulation.
The increased variability during AF leads to critical hemodynamic events of reduced blood flow or excessive pressure in the deepest cerebral circulation (arterioles and capillaries).

Results: percentile analysis

Heart rate response during AF on cerebral hemodynamics
The increased variability during AF leads to critical hemodynamic events of reduced blood flow or excessive pressure in the deepest cerebral circulation (arterioles and capillaries).
Results: hypoperfusions and hypertensive events

(a) Absolute frequency over 5000 beats of \( Q_{dm, left} \) and (b) hypertensive events \( P_c \) during AF.

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Heart rate response during AF on cerebral hemodynamics
Results: hypoperfusions and hypertensive events

- Absolute frequency over 5000 beats of (a) hypoperfusions ($Q_{dm,\text{left}}$) and (b) hypertensive events ($P_c$) during AF.
Results: total number of one-beat extreme events

<table>
<thead>
<tr>
<th>Heart Rate (bpm)</th>
<th>Hypoperfusions</th>
<th>Hypertensive events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q_{ICA,left}</td>
<td>Q_{MCA,left}</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>70</td>
<td>0</td>
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</tr>
<tr>
<td>90</td>
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<td>0</td>
</tr>
<tr>
<td>110</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>130</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Critical events (over 5000 beats) mainly occur in the distal region (rare episodes in the proximal region) and increase with HR.
### Hypoperfusions

<table>
<thead>
<tr>
<th>HR (bpm)</th>
<th>$Q_{ICA, left}$</th>
<th>$Q_{MCA, left}$</th>
<th>$Q_{dm, left}$</th>
<th>$Q_{pv}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1</td>
<td>2</td>
<td>196</td>
<td>124</td>
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<td>70</td>
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<td>0</td>
<td>321</td>
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<tr>
<td>90</td>
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<td>0</td>
<td>386</td>
<td>216</td>
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<tr>
<td>110</td>
<td>0</td>
<td>0</td>
<td>451</td>
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<tr>
<td>130</td>
<td>0</td>
<td>0</td>
<td>534</td>
<td>415</td>
</tr>
</tbody>
</table>

### Hypertensive events

<table>
<thead>
<tr>
<th>HR (bpm)</th>
<th>$P_a$</th>
<th>$P_{MCA, left}$</th>
<th>$P_{dm, left}$</th>
<th>$P_c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0</td>
<td>0</td>
<td>231</td>
<td>456</td>
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<td>70</td>
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<td>90</td>
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<tr>
<td>110</td>
<td>0</td>
<td>0</td>
<td>354</td>
<td>811</td>
</tr>
<tr>
<td>130</td>
<td>0</td>
<td>0</td>
<td>285</td>
<td>905</td>
</tr>
</tbody>
</table>

- Critical events (over 5000 beats) mainly occur in the distal region (rare episodes in the proximal region) and increase with HR.
The impact of AF on cerebral microcirculation is a potential mechanism into the genesis of AF-related cognitive impairment.

Repeated exposure to irregular and extreme values in AF promotes alteration of the hemodynamic patterns; potential damage either due to hypoperfusions (e.g., altered brain oxygenation) or hypertensive events (e.g., hemorrhagic episodes).

Role of HR during AF on cerebral hemodynamics:
- Distal critical episodes increase with HR
  \[ \Rightarrow \]
- no optimal HR target
  
  - At 50 bpm possible occurrence of proximal hypoperfusions
  
  \[ \Rightarrow \]
  - To overall minimize AF-induced impact
  \[ \Rightarrow \]
  

Compagnia di San Paolo is acknowledged for funding the present work within the Project CSTO160444 "Cerebral hemodynamics during atrial fibrillation".
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- Distal critical episodes increase with HR ⇒ no optimal HR target;
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Discussion & Conclusions

- The impact of AF on cerebral microcirculation is a potential mechanism into the genesis of AF-related cognitive impairment
  - Repeated exposure to irregular and extreme values in AF promotes an alteration of the hemodynamic patterns;
  - Potential damage either due to hypoperfusions (e.g., altered brain oxygenation) or hypertensive events (e.g., hemorrhagic episodes).

- Role of HR during AF on cerebral hemodynamics:
  - Distal critical episodes increase with HR ⇒ no optimal HR target;
  - At 50 bpm possible occurrence of proximal hypoperfusions;
  - To overall minimize AF-induced impact ⇒ 50<HR<70 bpm;
    worse cognitive outcomes for HR<50 bpm and HR>90 bpm.

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